CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

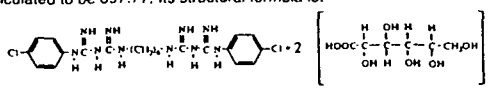
73695

DRAFT FINAL PRINTED LABELING

PERIOGARD®

(Chlorhexidine Gluconate Oral Rinse, 0.12%)

DESCRIPTION: PERIOGARD (Chlorhexidine Gluconate Oral Rinse, 0.12%) is an oral rinse containing 0.12% chlorhexidine gluconate [*N,N"*-bis (4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide di-*D*-gluconate] in a base containing water, 11.6% alcohol (%v/v), glycerin, PEG-40 sorbitan diisostearate, flavor, sodium saccharin, and FD&C Blue No. 1. PERIOGARD Oral Rinse is a near-neutral solution (pH range 5-7). Chlorhexidine gluconate is a salt of chlorhexidine and gluconic acid, with a molecular formula of $C_{22}H_{30}Cl_2N_{10}{\cdot}2C_6H_2O_7$ and a molecular weight calculated to be 897.77. Its structural formula is:



CLINICAL PHARMACOLOGY: PERIOGARD Oral Rinse provides microbicidal activity during oral rinsing. The clinical significance of 0.12% 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 a 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 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: PERIOGARD 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. PERIOGARD Oral Rinse has not been tested among patients with acute necrotizing ulcerative gingivitis (ANUG). For patients having coexisting gingivitis and periodontitis, see PRECAUTIONS.

CONTRAINDICATIONS: PERIOGARD Oral Rinse should not be used by persons who are known to be hypersensitive to chlorhexidine gluconate.

WARNINGS: The effect of PERIOGARD Oral Rinse on periodontitis has not been determined. An increase in supragingival calculus was noted in clinical testing with users of chlorhexidine gluconate oral rinse 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.

Rare hypersensitivity and generalized allergic reactions have also been reported. PERIOGARD Oral Rinse should not be used by persons who have a sensitivity to it or its components.

PRECAUTIONS

GENERAL

1. For patients having coexisting gingivitis and periodontitis, the presence or absence of gingival inflammation following treatment with PERIOGARD Oral Rinse should not be used as a major indicator of underlying periodontitis.

2. PERIOGARD 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 the chlorhexidine gluconate oral rinse users exhibited a measurable increase in facial anterior stain, compared to 35% of control users after six months; 15% of the chlorhexidine gluconate 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 the use of PERIOGARD 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 PERIOGARD Oral Rinse 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 a chlorhexidine gluconate oral rinse. Most patients accommodate to this effect with continued use of PERIOGARD Oral Rinse. No instances of permanent taste alteration due to the use of a chlorhexidine gluconate oral rinse have been reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

In a drinking water study in rats, carcinogenesis was not observed. The highest dose of chlorhexidine gluconate used in this study, 38 mg/kg/day, is at least 500 times the amount that would be ingested from the recommended daily dose of PERIOGARD Oral Rinse.

In two mammalian *in vivo* mutagenic studies with chlorhexidine gluconate, mutagenesis was not observed. The highest dose of chlorhexidine gluconate used in a mouse dominant lethal assay was 1000 mg/kg/day and in a hamster cytogenetics test was 250 mg/kg/day, i.e.> 3200 times the amount that would be ingested from the recommended daily dose of PERIOGARD Oral Rinse.

PREGNANCY: Pregnancy Category B. Reproduction and fertility studies with chlorhexidine gluconate have been conducted. No evidence of impaired fertility was observed in rats at doses up to 100mg/kg/day, and no evidence of harm to the fetus was observed in rats and rabbits at doses up to 300 mg/kg/day and 40 mg/kg/day, respectively. These doses are approximately 100, 300, and 40 times that which would result from a person's ingesting 30 mL of PERIOGARD Oral Rinse per day. Since controlled studies in pregnant women have not been conducted, the benefits of the drug in pregnant women should be weighed against possible risk to the fetus.

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 PERIOGARD Oral Rinse 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 that were over 100 times greater than that which would result from a person's ingesting 30 mL (2 capfuls) of PERIOGARD Oral Rinse per day.

PEDIATRIC USE: Clinical effectiveness and safety of PERIOGARD Oral Rinse have not been established in children under the age of 18.

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. No serious systemic adverse reactions associated with use of a 0.12% chlorhexidine gluconate oral rinse were observed in clinical testing.

Minor irritation and superficial desquamation of the oral mucosa have been noted in patients using chlorhexidine gluconate oral rinses, particularly among children.

Although there have been no reports of parotitis (inflammation or swelling of the salivary glands) among the users of chlorhexidine gluconate oral rinse in controlled clinical studies, transient parotitis has been reported in research studies with chlorhexidine-containing mouthrinses.

OVERDOSAGE: Ingestion of 1 or 2 ounces of PERIOGARD 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 PERIOGARD Oral Rinse is ingested by a small child or if signs of alcohol intoxication develop.

DOSAGE AND ADMINISTRATION: PERIOGARD Oral Rinse therapy should be initiated directly following a dental prophylaxis. Patients using PERIOGARD 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 on dosage cup) of undiluted PERIOGARD Oral Rinse. PERIOGARD Oral Rinse is not intended for ingestion and should be expectorated after rinsing.

HOW SUPPLIED: PERIOGARD Oral Rinse is supplied as a blue liquid in 16 fluid ounce amber plastic bottles with child-resistant closures and dosage cups. Store above freezing (32°F).

November 1993

Manufactured for Colgate Oral Pharmaceuticals by PACO Pharm., Lakewood, NJ 08701

Colgate Oral Pharmaceuticals, Inc.
a subsidiary of
Colgate-Palmolive Company
One Colgate Way
Canton, MA 02021 U.S.A.

APPROVED
JAN 14 1994

Colgate®

NDC 0126-0271-58

PERIOGARD®

(Chlorhexidine Gluconate Oral Rinse, 0.12%)

To open, squeeze sides of cap while turning. To close, turn until cap stops.

Directions for Use: Fill cap to "fill line" (1/2 ounce). Swish in mouth undiluted for 30 seconds twice daily, after breakfast and before bedtime after toothbrushing, expel remainder. 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 11.6% alcohol(%v/v), glycerin, PEG-40 sorbitan diisostearate, flavor, sodium saccharin, and FD&C Blue No 1.

Caution: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

PLACE PHARMACY LABEL HERE

Dispense in original container or in amber glass.

KEEP OUT OF REACH OF CHILDREN
STORE ABOVE FREEZING (32° F)

540 mL (18 fl oz)

Exp. Date
Batch #

Manufactured for Colgate Hoyt Gel-Kam by PACO Pharm. Lakewood, NJ 08701

Colgate Hoyt Gel-Kam
Division of Colgate-Palmolive Company
ONE COLGATE WAY
CANTON, MA 02021 U.S.A.

WHAT TO EXPECT WHEN USING PERIOGARD® (CHLORHEXIDINE GLUCONATE ORAL RINSE, 0.12%)

Your dentist has prescribed PERIOGARD (Chlorhexidine Gluconate Oral Rinse, 0.12%) to treat your gingivitis – to help reduce the redness and swelling of your gums, and to help you control any gum bleeding. Use PERIOGARD Oral Rinse regularly, as directed by your dentist, in addition to daily brushing and flossing.

PERIOGARD Oral Rinse may cause some tooth discoloration, or increase in tartar (calculus) formation, particularly in areas where plaque is more difficult to remove with normal brushing alone. It is important to see your dentist for removal of 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. PERIOGARD 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.
- Rare hypersensitivity and generalized allergic reactions have also been reported. PERIOGARD Oral Rinse should not be used by persons who have a sensitivity to it or its components.
- PERIOGARD 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 PERIOGARD Oral Rinse. After treatment with PERIOGARD Oral Rinse has ended, taste perception will be normal.
- To avoid taste interference, rinse with PERIOGARD Oral Rinse *after* meals. Do not rinse with water immediately after rinsing with PERIOGARD Oral Rinse as this will increase the bitter aftertaste.

If you have any questions or comments about PERIOGARD Oral Rinse, contact your dentist or pharmacist.

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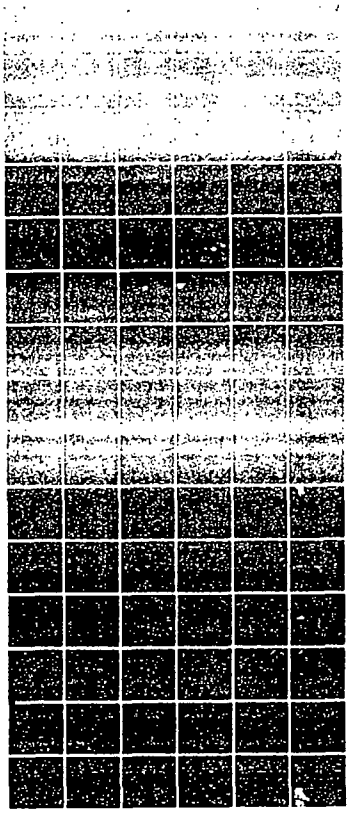

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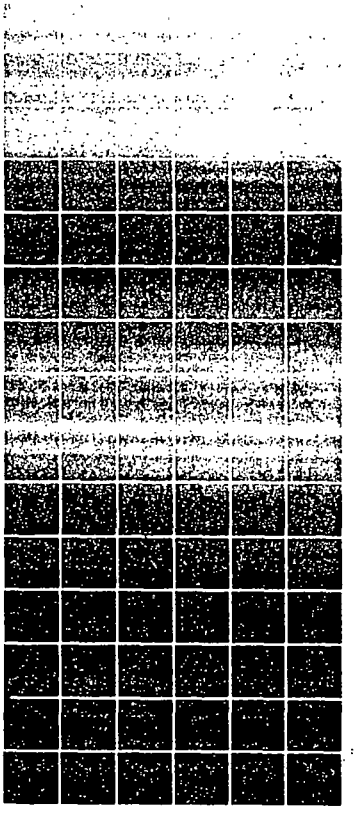

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