PRODUCT MONOGRAPH

PrPERIOGARD™ ALCOHOL FREE

Chlorhexidine Gluconate Oral Rinse 0.12% w/w, USP

Antigingivitis Oral Rinse

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Control #: 218608

Date of Revision:
March 8, 2019
Previous Approval Date:
December 19, 2017

PRODUCT MONOGRAPH

PrPERIOGARD™ ALCOHOL FREE

THERAPEUTIC CLASSIFICATION

Antigingivitis Oral Rinse

ACTIONS AND CLINICAL PHARMACOLOGY

PrPERIOGARD™ ALCOHOL FREE (0.12% Chlorhexidine Gluconate Oral Rinse, USP) provides antimicrobial activity during oral rinsing which is sustained between rinsings. Microbiological sampling of plaque has shown reduction of bacterial counts of certain assayed species, both aerobic and anaerobic, ranging from 54% - 97% through six months' use with a Chlorhexidine containing mouthrinse. The activity of Chlorhexidine in the oral cavity is promoted by binding to plaque, salivary pellicle, oral mucosa, and hard structures that may result in sustained release of up to 24 hours.

Use of a 0.12% chlorhexidine gluconate oral rinse in a six month clinical study did not result in any significant changes in bacterial resistance, overgrowth or potentially opportunistic organisms or other adverse changes in the oral microbial ecosystem. Three months after the use of a 0.12% Chlorhexidine Gluconate oral rinse 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.

Studies conducted on human subjects and animals demonstrate that chlorhexidine gluconate is poorly absorbed from the gastrointestinal tract. Excretion of chlorhexidine gluconate occurred primarily through feces (~90%). Less than 1% of the chlorhexidine gluconate ingested by these subjects was excreted in the urine.

INDICATIONS AND CLINICAL USE

PERIOGARD ALCOHOL FREE is indicated for use as part of a professional program for the treatment of moderate to severe gingivitis, and in addition for management of associated gingival bleeding and inflammation between dental visits. For patients having coexisting gingivitis and peridontitis, see PRECAUTIONS.

CONTRAINDICATIONS

Persons who are known to be hypersensitive to chlorhexidine gluconate or other formula ingredients should not use PERIOGARD ALCOHOL FREE (see composition).

WARNINGS

Use in Pregnancy
Preclinical studies with chlorhexidine gluconate have been conducted to evaluate reproduction and fertility. In rats and rabbits no evidence of fetal toxicity was observed at doses up to 300 mg/kg/day and 40 mg/kg/day respectively. Impaired fertility was not observed in rats at doses up to 100 mg/kg/day. These doses are approximately 40, 100 and 300 times that would result in ingesting 30 mL of PERIOGARD ALCOHOL FREE per day. Since controlled studies in pregnant women have not been conducted, the benefits of the use of the drug in pregnant women should be weighed against the possible risk of the fetus.

Nursing Mothers
Excretion of the drug substance in human milk has not been determined. Caution should be exercised when PERIOGARD ALCOHOL FREE is administered to a nursing woman.

No evidence of impaired or of toxic effects was observed to suckling pup rats from parturition and lactation studies 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 of PERIOGARD ALCOHOL FREE per day.

Pediatric Use
Clinical effectiveness and safety of PERIOGARD ALCOHOL FREE have not been established in children. The benefits of its use should be weighed against possible risks.

PRECAUTIONS

1. For patients having coexisting gingivitis and periodontitis, the presence or absence of gingival inflammation following treatment with PERIOGARD ALCOHOL FREE should not be used as an indicator of underlying Periodontitis.
2. PERIOGARD ALCOHOL FREE 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 tooth staining. Stain will be marked in patients who have heavier accumulations of unremoved plaque. Resulting stain from the use of PERIOGARD ALCOHOL FREE is not detrimental to the health of the gingivae or other oral tissues. Stain can be removed from most tooth surfaces by conventional prophylactic techniques.
3. Discretion should be used when prescribing to patients with anterior facial restorations having rough surfaces or margins. If natural staining proves too difficult to be removed from these surfaces by a professional dental prophylaxis, patients should be excluded from PERIOGARD ALCOHOL FREE treatment if the risk of permanent discoloration be unacceptable. Stain in these areas may be difficult to be removed by professional dental prophylaxis. In some instances staining may necessitate replacement of these restorations.
4. Some patients may experience an alteration in taste perception while undergoing treatment with a chlorhexidine gluconate oral rinse. Most patients undergoing treatment adapt to this effect with continued use. Rare instances of permanent

taste alteration following chlorhexidine gluconate oral rinse use have been reported via postmarketing surveillance.

5. Rinsing of the oral cavity, eating or drinking after using PERIOGARD ALCOHOL FREE should be avoided for approximately 30 minutes to provide maximum effectiveness. Rare instances of permanent taste alteration following chlorhexidine gluconate oral rinse have been reported via postmarketing surveillance.

ADVERSE REACTIONS

Common sides effects associated with the use of a 0.12% chlorhexidine gluconate oral rinses are (1) an increase in staining of teeth and other oral surfaces, (2) an increase in calculus formation, and (3) and alteration in taste perception (see PRECAUTIONS). Oral irritation and local allergy-type symptoms have been spontaneously reported as side effects associated with use of chlorhexidine gluconate rinses. 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 1.0%.

Among postmarketing reports, the most frequently reported oral mucosal symptoms associated with chlorhexidine gluconate oral rinse are stomatitis, gingivitis, 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 rinses. There have been cases of parotid gland swelling and inflammation of the salivary glands (sialadentitis) reported in patients using chlorhexidine gluconate oral rinse.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Ingestion of 1 to 2 ounces (30 to 60 mL) of PERIOGARD ALCOHOL FREE by a small child (~ 10 kg body weight) may result in gastric distress and nausea. Medical attention should be sought if more than 4 ounces (120 mL) of PERIOGARD ALCOHOL FREE is ingested by a small child.

For management of suspected drug overdose, contact your regional poison control centre.

DOSAGE AND ADMINISTRATION

PERIOGARD ALCOHOL FREE therapy should be administered immediately following a dental prophylaxis. Those patients using PERIOGARD ALCOHOL FREE should be re-evaluated and given a complete professional prophylaxis at intervals no longer than six months. As necessary, patients should be referred for periodontal consultation.

The recommended usage is twice daily of oral rinsing for 30 seconds, morning and evening, subsequent to tooth brushing. Usual dosage is ½ Fl. Ounce (15 mL mark on dosage cap/cup) of undiluted PERIOGARD ALCOHOL FREE. PERIOGARD ALCOHOL FREE is not intended for ingestion. Product should be expectorated after rinsing. Patients should not rinse with water or other mouth-washes, brush teeth or eat immediately after rinsing with PERIOGARD ALCOHOL FREE.

The recommended initial regimen of therapy is three months. Patients should be recalled for evaluation at the conclusion of the three month course of therapy. At the time of the evaluation visit, the dental professional should consider the following points:

- Evaluate progress, remove any resulting stain, and reinforce proper oral care practice.
- Should gingival inflammation and bleeding be controlled at this interval, cease PERIOGARD ALCOHOL FREE therapy. Re-evaluate the patient in three months to assess gingival health.
- If gingival inflammation and bleeding have continued, PERIOGARD ALCOHOL FREE therapy should be prescribed for an additional three months. A subsequent three-month recall for evaluation should be scheduled.
- Evaluate the patient undergoing therapy for evidence of epithelial irritation, desquamation and parotitis.

Presented on the following page is a generally accepted grading system which may be used in severity of gingivitis.

GINGIVAL INDEX (GI) Loe and Silness

GRADE	DESCRIPTION
1	NORMAL gingiva, no inflammation, no discoloration, no bleeding.
2	MILD inflammation, slight color change, mild alteration of gingival surface. No bleeding.
3	MODERATE inflammation, erythema, swelling, bleeding on probing or when pressure is applied.
4	SEVERE inflammation, severe erythema and swelling, tendency toward spontaneous hemorrhage, some ulceration.

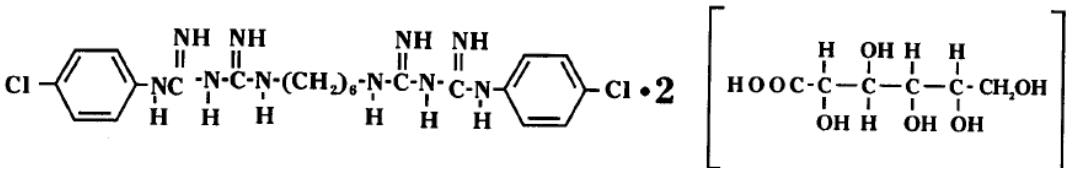
If the patient is generally compliant with the prescribed regimen, an occasional missed dose can be ignored.

PHARMACEUTICAL INFORMATION

Proper Name: Chlorhexidine Gluconate (U.S.A.N.)

Chemical Name: [N, N" bis(4 chlorophenyl) 3, 12 diimino 2,4,11,13 tetraazatetradecanediimideamide di D gluconate]

Structure:



Molecular Formula: $C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$

Molecular Weight: 897.77

Description:
Chlorhexidine is a cationic bis-biguanide usually sold as a gluconate salt. The drug substance is a stable molecule, undergoing cleavage in strongly alkaline media. At 19-21% w/v chlorhexidine gluconate solution is colorless to pale straw-colored and is almost odourless (BP).

The CAS Registry Number of chlorhexidine gluconate is 18472-51-0. Chlorhexidine gluconate is a salt of chlorhexidine and gluconic acid.

Composition:
PERIOGARD ALCOHOL FREE (0.12% w/w Chlorhexidine Gluconate Oral Rinse) is an oral rinse containing 0.12% chlorhexidine gluconate in a base containing, FD&C Blue No. 1, flavour, glycerin, sorbitol, polyethylene glycol-40 hydrogenated castor, propylene glycol, cetylpyridinium chloride and water. PERIOGARD ALCOHOL FREE is a near neutral solution (pH range 5-7).

Stability and Storage Recommendations: Store above freezing (15 – 25 ºC).

Incompatibilities: None known.

Special Instructions: None

AVAILABILITY OF DOSAGE FORMS

[PR]PERIOGARD™ ALCOHOL FREE Oral Rinse is supplied as a clear, light blue liquid in 470 mL amber plastic bottles with child-resistant dosage cap/cup.

INFORMATION FOR THE CONSUMER (Product Labelling)

WHAT TO EXPECT WHEN USING PERIOGARD ALCOHOL FREE:

Your dentist has prescribed ^{Pr}PERIOGARD^{TM} ALCOHOL FREE (0.12% w/w Chlorhexidine Gluconate) to treat your gingivitis, to help reduce the redness and swelling of your gums, and to also help you control any gum bleeding. Use PERIOGARD ALCOHOL FREE regularly, as directed by your dentist, in addition to daily brushing and flossing. Spit out after use; PERIOGARD ALCOHOL FREE Oral Rinse should not be swallowed.

PERIOGARD ALCOHOL FREE 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 ALCOHOL FREE Oral Rinse cause permanent discoloration of some front tooth fillings.
- To minimize discoloration, you should brush and floss daily, emphasising areas which begin to discolour.
- Local hypersensitivity and generalized allergic reactions have also been reported. PERIOGARD ALCOHOL FREE Oral Rinse should not be used by persons who have a sensitivity to it or its components.
- PERIOGARD ALCOHOL FREE Oral Rinse may taste bitter to some patients and affect how foods and beverages taste. This will become less noticeable in most cases with continued use of PERIOGARD ALCOHOL FREE Oral Rinse. <u>In some cases, the taste alteration is permanent.</u>
- To avoid taste interference, rinse with PERIOGARD ALCOHOL FREE Oral Rinse after meals. Do not rinse with water or other mouthwashes immediately after rinsing with PERIOGARD ALCOHOL FREE Oral Rinse, as this will increase the bitter aftertaste.

If you have any questions or comments about PERIOGARD ALCOHOL FREE, contact your dentist or pharmacist.

PHARMACOLOGY

Human Clinical Trials

The efficacy of 0.12% chlorhexidine gluconate in the treatment and prevention of gingivitis is supported by three pivotal clinical trials and in several supporting clinical studies. The pivotal clinical studies with PERIOGARD (original formula with alcohol) are summarized in the chart presented below.

HUMAN CLINICAL TRIALS

Study Location	Duration	No. Patients	Age	Sex	Regimen	Plaque Index Scores	Gingival Index Scores	Bleeding Sites
San Antonio TX	3 Mo.	597	18-60	M&F	According to Package Instructions 15 mL bid	36.1%	27.8-45.8%	48.4%
North Field NJ	6 Mo.	430	18-60	″	Regimen	60.9%	33.5-45.4%	41.6-52.2%
London ON	2 yr.	456	18-72	″	″	34.6–56.4%	36.9%	50.3%

*Results presented in the above chart are data obtained for the final examination at completion of test product use. The figures are expressed as covariance adjusted percent reduction versus the placebo product used in clinical testing (results are reported as a range where duplicate examiners were used). All reductions are significantly different from placebo ($p<0.05$: nonparametric Wilcoxon pair test).

The results of these studies support that 0.12% Chlorhexidine Gluconate is effective in reducing both plaque accumulation and the incidence and severity of gingivitis, as well as reducing the number of bleeding sites.

MICROBIOLOGY

In Vitro

Chlorhexidine has a wide spectrum of activity against both gram positive and gram negative organisms. In a microbicidal effect In Vitro study, following a thirty second exposure to a 0.12% chlorhexidine containing oral rinse, a 99.9% reduction was observed in the following group of micro-organisms: Actinomyces viscosus, Candida albicans, Staphylococcus aureus, Streptococcus mutans, Streptococcus sanguis, Fusobacterium nucleatum, Neisseria sica, Pseudomonas aeruginosa, Veillonella parvula.

In Vivo

Results of in vivo studies indicate that use of a 0.12% chlorhexidine containing mouth rinse was associated with reductions in the number of microbes in the plaque without change in the bacterial sensitivity. No significant changes in bacterial sensitivity. No significant changes in bacterial resistances, overgrowth of potentially opportunistic organisms or other adverse changes in the oral microbial ecosystem were observed in the six month clinical study of 0.12% chlorhexidine. Three months after chlorhexidine gluconate was discontinued, the number of bacteria in plaque had returned to baseline levels and resistance of plaque bacteria to chlorhexidine gluconate was equivalent to that of baseline.

Minimum Inhibitory Concentrations (MICs) for chlorhexidine, were determined on isolates of streptococci and actinomyces from patients during six months use of a chlorhexidine containing mouthrinse and three months after patients discontinued use of the product. Changes in the bacterial sensitivity due to exposure to chlorhexidine were infrequent and sporadic and had returned to baseline values three months after cessation of product use.

Pharmacodynamics

Two clinical studies examined the dose response relationships and confirmed earlier animal studies. One short term study was conducted with 0.10%, 0.20% and 0.05% chlorhexidine gluconate solutions. The results show that solutions containing 0.10% and 0.20% chlorhexidine demonstrate equal efficacy as measured by plaque reduction. However, the solution containing 0.05% chlorhexidine was less effective.

In a three month anti gingivitis study, the efficacy was found to be equal for 0.10% and 0.20% chlorhexidine gluconate solutions. However, consistent with the increase in concentration of the active ingredient, discoloration of the tooth and tongue increased. Therefore, a concentration of 0.12% was established based on optimal efficacy and the minimization of side effects.

Pharmacokinetics

Oral Retention / Desorption

Studies conducted with a 0.12% chlorhexidine gluconate oral rinse solution indicated that approximately 30% of the active ingredient is retained in the oral cavity following rinsing. After single uses of solutions containing 0.12% and 0.06% chlorhexidine gluconate, subjects retained an average of 6.3 and 2.7 mg (mean) of chlorhexidine orally.

Ingestion/ Absorption / Excretion

PERIOGARD ALCOHOL FREE is to be used solely as a topical oral rinse, and not to be ingested. Studies conducted on human subjects and animals demonstrate that chlorhexidine gluconate is poorly absorbed from the gastrointestinal tract. A study with five normal male volunteers indicates that the mean plasma level of chlorhexidine gluconate reached a peak of 0.206 µg/g in humans 30 minutes after ingestion of a 300 mg dose of the drug. Detectable levels of chlorhexidine were not present in the plasma of these subjects 12 hours after ingestion. Excretion of chlorhexidine occurred primarily through feces (~90%). Less than 1% of chlorhexidine gluconate ingested by these subjects was excreted in the urine.

TOXICOLOGY

Acute Toxicity Studies

The oral LD50 of chlorhexidine gluconate is estimated as 1.476 g/kg in rats and 0.122 g/kg in rabbits. The oral LD50 of a chlorhexidine containing mouthrinse was estimated at >20 g/kg in rats.

Chronic and Subchronic Toxicity Studies

Accumulation of foamy macrophages in the mesenteric lymph nodes of rats was the only consistently observed finding in eight subchronic and chronic toxicity studies. Representative lesions were evaluated by two independent pathologists. Based upon

evaluation, these lesions did not represent a toxic effect. This is supported by observations that

1) macrophages do not contain bacteria, therefore, indicating that a significant alteration in the intestinal flora does not occur,
2) Reactions are not associated with increased morbidity or mortality
3) Reactions do not become progressively more severe with continued exposure to the drug substance and,
4) After discontinuation, the reaction is reversible.

Reproduction and Teratology

No evidence of impaired fertility was observed in rats or rabbits in studies with chlorhexidine containing mouthrinse. In rabbits, receiving a daily 40 mg/kg dose of chlorhexidine by gavage, an apparent embryotoxic effect was observed. Embryotoxic effects were also observed in rats ingesting a 300 mg/kg dose of chlorhexidine from their diet each day. These doses are approximately 140 to 1040 times, respectively, the daily ingestion expected from the use of PERIOGARD ALCOHOL FREE used according to the recommended dosage. Since controlled studies in pregnant women have not been conducted, the benefits of the use of the drug in pregnant women should be weighed against the possible risk to the fetus.

Carcinogenicity

There are no reports of any evidence of carcinogenicity in two rat studies conducted in which chlorhexidine was administered to animals in their drinking water. Each study was two years in duration and the delivered dosage of chlorhexidine during these studies were to 200 mg/kg/day.

Mutagenicity

When chlorhexidine was evaluated by the dominant lethal assay in mice and micronucleus assay in hamsters, there was no observed evidence of mutagenicity.

Immediate Hypersensitivity

Attempts to induce or elicit immediate hypersensitivity to chlorhexidine gluconate in guinea pigs, rabbits, rats and man were conducted. There was no evidence of immediate hypersensitivity observed in any of these tests.

Other Studies

The emetic dose, irritation and sensitization potentials have been determined for 0.12% chlorhexidine gluconate oral rinse. 0.12% chlorhexidine gluconate oral rinse has an emetic ED50 of approximately 13 mL/kg (dogs/oral route of administration), is only slightly irritating to the eye (rabbits), and was not irritating to the oral mucosa (dogs). In addition, the chlorhexidine containing mouthrinse does not include delayed contact sensitization.

REFERENCES

1. Grossman, E., Reiter, G., Sturzenberger, O., De La Rosa, M., Dickinson, T., Flrretti, G., Ludlam, G., Meckel, A.: Six Month Study of the Effects of a Chlorhexidine Mouthrinse on Gingivitis in Adults. Journal Peridontol Research 1986, 21 (Supplement 16): 33-43.

2. Briner, W., Grossman, E. Buckner, R., Rebitski, G., Sox, T., Setser, R., Ebert, M.: Effect od Chlorhexidine Gluconate Mouthrinse of Plaque Bacteria. Journal of Periodontol Research 1986, 21 (Supplement 16): 33-43.

3. Briner, W., Grossman, E., Buckner, R., Rebitski, G., Sox, T., Setser, R., Ebert, M.: Assessment of Susceptibility of Plaque Bacteria to Chlorhexidine After Six Months' Oral Use. Journal of Periodontol Research 1986, 21 (Supplement 16): 53~59.

4. Löe, H., Rindom-Schiott, C., Glavind, J., Karring, T.; Two Years Oral Use of Chlorhexidine in Man. I. General Design and Clinical Effects. Journal of Periodontol Research 1976, 11: 135~144.

5. Löe, H., Rindom-Schiött, C., Löe, H.: Two Year Oral Use of Chlorhexidine in Man. II. He Effect on Salivary Bacterial Flora. Journal of Periodontol Research 1976, 11: 145~152.

6. Warner, V., Lynch, D., Kim, K., Grunewald, G.: Quantitative structure-activity relationships for biguanides, carbamimidates, and bisbiguanides as inhibitors of Streptococcus mutans No. 6715. J Med Chem. 1979 Apr; 22(4):359-66