

# PRODUCT MONOGRAPH

**PrPERICHLOR®**

**PrPERICHLOR® WITHOUT ALCOHOL**

Chlorhexidine Gluconate Mouthwash  
0.12%  
BP

**Antigingivitis Oral Rinse**

**Pendopharm, Division of Pharmascience Inc.**

6111 Royalmount Ave., Suite 100  
Montréal, Canada  
H4P 2T4

Date of Revision:  
October 10, 2019

PERICHLOR® is a registered trademark of Pharmascience Inc.

Submission Control No: 223243

## **PrPERICHLOR®**

### **PrPERICHLOR® WITHOUT ALCOHOL**

Chlorhexidine Gluconate Mouthwash

0.12%

BP

#### **ACTIONS, CLINICAL PHARMACOLOGY**

PERICHLOR and PERICHLOR WITHOUT ALCOHOL (0.12% Chlorhexidine Gluconate Mouthwash) provide antimicrobial activity during oral rinsing which is maintained between rinsings. Microbiologic sampling of plaque has shown a general reduction of both aerobic and anaerobic bacterial counts ranging from 54-97% through six months' clinical use. Rinsing with PERICHLOR and PERICHLOR WITHOUT ALCOHOL inhibits the buildup and maturation of plaque by reducing certain microbes regarded as gingival pathogens, thereby reducing gingivitis<sup>1,4,5</sup>. Chlorhexidine Gluconate Mouthwash provided antimicrobial activity during rinsing and for several hours thereafter.

No significant changes in bacterial sensitivity, overgrowth of potentially opportunistic organisms or other adverse changes in the oral microbial flora were observed following the use of Chlorhexidine Gluconate Mouthwash for six months. Three months after Chlorhexidine Gluconate Mouthwash use was discontinued, the number of bacteria in plaque had returned to pre-treatment levels and sensitivity of plaque bacteria to chlorhexidine gluconate remained unchanged.

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

#### **INDICATIONS AND CLINICAL USE**

PERICHLOR and PERICHLOR WITHOUT ALCOHOL (0.12% Chlorhexidine Gluconate Mouthwash) are indicated for use as part of a professional program for the treatment of moderate to severe gingivitis, and for management of associated gingival bleeding and inflammation between dental visits. For patients having coexisting gingivitis and periodontitis, see PRECAUTIONS.

## **CONTRAINDICATIONS**

PERICHLOR and PERICHLOR WITHOUT ALCOHOL (0.12% Chlorhexidine Gluconate Mouthwash) should not be used by persons who are known to be hypersensitive to chlorhexidine gluconate or other formula ingredients.

## **WARNINGS**

### **USE IN PREGNANCY:**

Reproduction and fertility studies with chlorhexidine gluconate have been conducted. No evidence of impaired fertility was observed in male and female rats at doses up to 100 mg/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 ingesting 30 mL (2 capfuls) of PERICHLOR or PERICHLOR WITHOUT ALCOHOL (0.12% Chlorhexidine Gluconate Mouthwash) per day. Since controlled studies in pregnant women have not been conducted, the benefits of use of the drug in pregnant women should be weighed against possible risk to the fetus.

### **BREASTFEEDING MOTHERS:**

It is not known whether this drug is excreted in human milk. 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 the dose which would result if a person ingested the entire recommended dose of PERICHLOR or PERICHLOR WITHOUT ALCOHOL (0.12% Chlorhexidine Gluconate Mouthwash) on a daily basis.

### **USE IN CHILDREN:**

Since the safety and efficacy of Chlorhexidine Gluconate Mouthwash in children has not yet been fully established, the benefits of its use should be weighed against the possible risks.

## **PRECAUTIONS**

1. For patients having coexisting gingivitis and periodontitis, the absence of gingival inflammation following treatment with PERICHLOR or PERICHLOR WITHOUT ALCOHOL (0.12% Chlorhexidine Gluconate Mouthwash) may not be indicative of the absence of underlying periodontitis. Appropriate treatment of periodontitis is therefore indicated.
2. PERICHLOR and PERICHLOR WITHOUT ALCOHOL may cause staining of oral surfaces such as the film on tooth surfaces, restorations, and the dorsum of the tongue. Stain will be more pronounced in patients who have heavier accumulations of un-removed plaque.

Stain resulting from use of PERICHLOR or PERICHLOR WITHOUT ALCOHOL does not adversely affect the health of gingivae or other oral tissue. 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 treating patients with exposed root surfaces or anterior facial restorations with rough surfaces or margins. If natural stains cannot be removed from these surfaces by a dental prophylaxis, patients should be excluded from PERICHLOR and PERICHLOR WITHOUT ALCOHOL treatment if the risk of permanent discolouration is unacceptable. Stains in these areas may be difficult to remove by dental prophylaxis and on rare occasions may necessitate replacement of these restorations.

3. A few patients may experience an alteration in taste perception while undergoing treatment with PERICHLOR or PERICHLOR WITHOUT ALCOHOL. Most of these patients accommodate to this effect with continued use of Chlorhexidine Gluconate Mouthwash. Rare instances of permanent taste alteration following Chlorhexidine Gluconate Mouthwash use have been reported via post-marketing product surveillance.
4. For maximum effectiveness the patient should avoid rinsing their mouth (with water or other mouthwashes), brushing their teeth, eating or drinking for about 30 minutes after using PERICHLOR or PERICHLOR WITHOUT ALCOHOL.

## **ADVERSE REACTIONS**

No serious systemic reactions associated with use of 0.12% Chlorhexidine Gluconate Mouthwash were observed in clinical testing. However, some adverse reactions have been reported in studies with Chlorhexidine Gluconate Mouthwash or other chlorhexidine containing mouth rinses. The most common side effects associated with chlorhexidine gluconate mouthwash are (1) an increase in staining of oral surfaces, (2) an increase in supragingival tartar (3) an alteration in taste perception to which most patients accommodate (see PRECAUTIONS).

Epithelial irritation and superficial desquamation of the oral mucosa have been noted in studies of children using 0.12% chlorhexidine gluconate which were reversible upon discontinuation.

There have been rare cases of parotid gland swelling and inflammation of the salivary glands, in patients using Chlorhexidine Gluconate Mouthwash.

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, ulcerations, erythma, 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 Mouthwash are stomatitis, gingivitis, glossitis, ulcer, dry mouth, hypesthesia, glossal edema, and paresthesia.

#### **REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

#### **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

Ingestion of 30 or 60 mL of PERICHLOR or PERICHLOR WITHOUT ALCOHOL (0.12% Chlorhexidine Gluconate Mouthwash) by a small child (10 kg or less body weight) might result in gastric distress, including nausea, or signs of alcohol intoxication. Medical attention should be sought if more than 120 mL of PERICHLOR or PERICHLOR WITHOUT ALCOHOL is ingested by a small child or signs of alcohol intoxication develop.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

#### **DOSAGE AND ADMINISTRATION**

PERICHLOR or PERICHLOR WITHOUT ALCOHOL (0.12% Chlorhexidine Gluconate Mouthwash) therapy should be initiated directly following a dental prophylaxis. Patients using PERICHLOR or PERICHLOR WITHOUT ALCOHOL should be reevaluated and given a thorough prophylaxis at intervals no longer than six months; they should be referred for periodontal consultation as necessary. Recommended use is twice daily oral rinsing for 30 seconds, morning and evening after tooth brushing. Usual dosage is 15 mL

(3 tsp) of undiluted PERICHLOR or PERICHLOR WITHOUT ALCOHOL. PERICHLOR and PERICHLOR WITHOUT ALCOHOL are not intended for ingestion and should be expectorated after rinsing. Rinsing the mouth (with water or other mouthwashes), brushing teeth, or eating or drinking should be avoided for about 30 minutes after using PERICHLOR or PERICHLOR WITHOUT ALCOHOL.

The suggested initial course of therapy is 3 months, at which time patients should be recalled for evaluation. At the time of the recall visit, the dental professional should:

- Evaluate progress, remove any stain, and reinforce proper home care techniques.
- If gingival inflammation and bleeding is controlled, discontinue PERICHLOR or PERICHLOR WITHOUT ALCOHOL therapy and recall the patient in three months to assess gingival health.
- If gingival inflammation and bleeding persist, continue PERICHLOR or PERICHLOR WITHOUT ALCOHOL therapy for an additional 3 months and schedule a three-month recall for evaluation.
- Evaluate for evidence of epithelial irritation, desquamation and parotitis.

The following generally accepted grading scheme may be of use in evaluating the severity of gingivitis.

### Loe and Silness

#### GINGIVAL INDEX (GI)

Grade	Description
1	<b>Normal</b> gingival, no inflammation, no discoloration, no bleeding.
2	<b>Mild</b> inflammation, slight colour change, mild alteration of gingival surface. No bleeding.
3	<b>Moderate</b> inflammation, erythema, swelling, bleeding on probing or when pressure applied.
4	<b>Severe</b> inflammation, severe erythema and swelling, tendency toward spontaneous haemorrhage, some ulceration.

An occasional missed dose can be ignored if the patient is generally compliant with the prescribed regimen.

#### AVAILABILITY OF DOSAGE FORM

PERICHLOR (0.12% Chlorhexidine Gluconate Mouthwash) is supplied as a clear bluish liquid with no visible precipitate packed in HDPE white round bottles of 475 mL.

PERICHLOR WITHOUT ALCOHOL (0.12% Chlorhexidine Gluconate Mouthwash) is supplied as a clear liquid with no visible precipitate packed in HDPE white round bottles of 475 mL.

**Composition**

PERICHLOR contains Chlorhexidine Gluconate Mouthwash 0.12% and the following non-medicinal ingredients: Ethanol, FD&C Blue No.1, Glycerin, Hydroxyethylcellulose, Peppermint Flavour, Purified Water and Xylitol Crystals.

PERICHLOR WITHOUT ALCOHOL contains Chlorhexidine Gluconate Mouthwash 0.12% and the following non-medicinal ingredients: Glycerin, Hydroxyethylcellulose, Purified Water, Hydrochloric Acid and Xylitol Crystals

**Stability and storage**

Store between 15°C and 25°C.

**Incompatibilities**

PERICHLOR and PERICHLOR WITHOUT ALCOHOL are not to be mixed/diluted with any other product.

**Special Instructions**

None

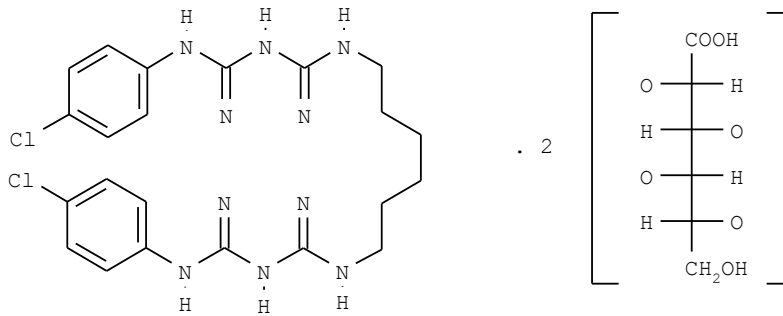
## PHARMACEUTICAL INFORMATION

### DRUG SUBSTANCE

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

**Chemical Name:** 1,1'-hexamethylene bis [5- (p-chlorophenyl) biguanide] di-D-gluconate

**Structure:**



**Molecular Weight:** 897.8 g/mol

**Description:** Chlorhexidine has basic character and exists in the di-cationic form at physiologic pH. The two protonic positive charges become somewhat localized on the biguanide portion of the molecule. Both pKa's are reported as  $10.78 \pm 0.06$ . The gluconate salt is soluble in excess of 70% (w/v) in water at 20°C. At 19\_21% w/v chlorhexidine gluconate solution is colourless to pale straw coloured and is odourless to almost odourless (British Pharmacopoeia).



## INFORMATION FOR THE CONSUMER

### WHAT TO EXPECT WHEN USING PERICHLOR OR PERICHLOR WITHOUT ALCOHOL

Your dentist has prescribed PERICHLOR or PERICHLOR WITHOUT ALCOHOL to treat your gingivitis – to help reduce the redness and swelling of your gums, and also to help you control any gum bleeding. Use PERICHLOR or PERICHLOR WITHOUT ALCOHOL regularly, as directed by your dentist, in addition to daily brushing and flossing. Do not swallow PERICHLOR or PERICHLOR WITHOUT ALCOHOL. PERICHLOR and PERICHLOR WITHOUT ALCOHOL may cause some tooth discolouration or increases in tartar (calculus) formation, particularly in areas where plaque is more difficult to remove with normal brushing alone. It is important to do a thorough job of cleaning your teeth and to see your dentist at least every six months, or more frequently if your dentist advises.

- Both stain and tartar can be removed by your dentist or hygienist. PERICHLOR and PERICHLOR WITHOUT ALCOHOL may cause permanent discolouration of some front-tooth fillings. To minimize discolouration, you should brush and floss daily, emphasizing areas which begin to discolour. In some cases discolouration may be permanent.
- PERICHLOR and PERICHLOR WITHOUT ALCOHOL should not be used by persons who have a sensitivity to chlorhexidine gluconate.
- PERICHLOR and PERICHLOR WITHOUT ALCOHOL may taste bitter to some patients and may affect the taste of foods and beverages. This will become less noticeable in most cases with continued use of PERICHLOR or PERICHLOR WITHOUT ALCOHOL. To avoid taste interference, rinse with PERICHLOR or PERICHLOR WITHOUT ALCOHOL after meals. Do not rinse with water or other mouth rinses immediately after rinsing with PERICHLOR or PERICHLOR WITHOUT ALCOHOL.
- For maximum effectiveness avoid rinsing your mouth, brushing your teeth, eating or drinking for about 30 minutes after using PERICHLOR or PERICHLOR WITHOUT ALCOHOL

If you have any questions or comments about PERICHLOR or PERICHLOR WITHOUT ALCOHOL, contact your dentist or health care professional.

### COMPOSITION

PERICHLOR contains chlorhexidine gluconate Mouthwash 0.12% and the following non-medicinal ingredients: Ethanol, FD&C Blue No.1, Glycerin, Hydroxyethylcellulose, Peppermint Flavour, purified water and xylitol crystals.

PERICHLOR WITHOUT ALCOHOL contains Chlorhexidine Gluconate Mouthwash 0.12% and the following non-medicinal ingredients: Glycerin, Hydroxyethyl Cellulose, purified water, hydrochloric acid and xylitol crystals

## STABILITY AND STORAGE RECOMMENDATIONS

Store between 15° and 25°C.

## INCOMPATIBILITIES

PERICHLOR and PERICHLOR WITHOUT ALCOHOL are not to be mixed/diluted with any other product.

## PHARMACOLOGY:

### HUMAN CLINICAL TRIALS:

The efficacy of 0.12% Chlorhexidine Gluconate Mouthwash in the treatment and prevention of gingivitis has been supported in three pivotal clinical trials and in several supporting studies. The pivotal clinical studies are summarized in the following chart:

Study Location	Study Duration	No. Patients	Age	Sex	Usage Regimen	Reduction in*		
						Plaque Index Scores	Gingival Inflammation Index Scores	Bleeding Sites
San Antonio TX	3 Mon.	597	18-60	M&F	According to pkg. instructions 15 mL bid	36.1%	27.8%-45.8%	48.4%
Northfield NJ	6 Mon.	430	18-60			60.9%	33.5%-45.4%	41.6%-52.2%
London ON	2 Yr.	456	18-72			34.6%-56.4%	39.6%	50.3%

\*Results shown are those obtained for the final examination at completion of test product use. The data are expressed as covariance adjusted % reduction vs. placebo; a range is reported when there were duplicate examiners. All reductions were significantly different from placebo ( $p < 0.05$ ; nonparametric Wilcoxon pair test)

The results of these studies support that 0.12% Chlorhexidine Gluconate Mouthwash 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

Because of its nonspecific mechanism of action, chlorhexidine has a wide range of anti microbial activity against both Gram-positive and Gram-negative bacteria. An *in-vitro* study of the microbicidal effect of 0.12% Chlorhexidine Gluconate Mouthwash following

a 30 second exposure resulted in greater than a 99.9% reduction in the following micro-organisms: *Actinomyces viscosus*, *Candida albicans*, *Staphylococcus aureus*, *Streptococcus mutans*, *Streptococcus sanguis*, *Fusobacterium nucleatum*, *Neisseria sicca*, *Pseudomonas aeruginosa*, *Veillonella parvula*.

### **In Vivo**

To determine the efficacy of Chlorhexidine Gluconate Mouthwash *in vivo*, various bacteria in the microbial flora of plaque were assayed in subjects who had used either Chlorhexidine Gluconate Mouthwash or a placebo.

During six months' Chlorhexidine Gluconate Mouthwash use, 2,3 subjects showed reductions in total load/tooth, streptococci and actinomyces ranging from 54% to 97%. *Neisseria* and *fusobacteria* were not detected in over half of the subjects assayed. No changes in numbers of yeast-like organisms and Gram-negative enterics were observed. There were no adverse changes in the oral microbial flora. Three months following cessation of treatment, the reductions observed during mouth rinsing were no longer evident, indicating no "carryover" effect. The results were interpreted as indicating that the use of Chlorhexidine Gluconate Mouthwash was associated only with a decrease in the number of microbes in plaque and no change in bacterial sensitivity.

Another study was conducted to investigate whether changes occurred in resistance to chlorhexidine which might limit efficacy of the mouth rinse, and if such changes occurred, whether they dissipated or disappeared after cessation of use of the mouth rinse. Minimum Inhibitory Concentrations (MIC's) for chlorhexidine were determined on isolates of streptococci and actinomyces obtained from patients during six months' use of the mouth rinse and three months after cessation of use of the mouth rinse<sup>5</sup>. Changes in bacterial sensitivity due to exposure to chlorhexidine were slight, sporadic and had returned to pre-treatment values three months after product usage was discontinued.

These results support that Chlorhexidine Gluconate Mouthwash usage does not result in significant changes in plaque bacterial resistance and does not cause significant changes in the plaque flora.

### **Pharmacodynamics**

Two clinical studies examined dose-response relationships and confirmed earlier animal studies. One short term study demonstrated equal efficacy, as measured by plaque reduction, for 0.10% and 0.20% chlorhexidine gluconate solutions while a 0.05% chlorhexidine gluconate solution was less effective. In a three month study, anti-gingivitis efficacy was equal for 0.12% and 0.20% chlorhexidine gluconate mouth rinses. However, tooth and tongue discolouration increases with chlorhexidine concentration in both studies. Therefore, the chlorhexidine gluconate concentration for Chlorhexidine Gluconate Mouthwash was set at 0.12% to optimize efficacy while minimizing side effects.

The effect of duration and frequency of rinsing on plaque formation and tooth and tongue discolouration was examined in another 88 day study. The data demonstrated that shorter, more frequent rinsing (i.e. 2 x 30 sec.) provided optimal efficacy as compared to longer, less frequent rinsing (i.e. 1 x 60 sec.).

## **Pharmacokinetics**

### **1. Oral Retention/Desorption**

Approximately 30% of the chlorhexidine present in the mouth rinse is retained in the oral cavity after rinsing. The amount retained was directly related to drug concentration, with an average of 6.3 and 2.7 mg (mean) of chlorhexidine being retained orally after a single use of a mouth rinse containing 0.12% and 0.06% chlorhexidine gluconate, respectively. The release rate of chlorhexidine from oral surfaces was similar for both treatments. Based on morning/evening rinses, previous exposure to a chlorhexidine-containing mouth rinse was observed to have little effect on subsequent retention of chlorhexidine.

### **2. Ingestion/Absorption/Excretion**

0.12% Chlorhexidine Gluconate Mouthwash is to be used topically as an oral rinse, not to be ingested. Studies were conducted to study its metabolic pathway in the event of oral ingestion.

Human studies using radiological markers indicated that chlorhexidine gluconate is poorly absorbed from the gastrointestinal tract. This is in agreement with the findings from animal studies. Among five normal male volunteers, GI transit time was 31 to 53 hours as indicated by radio-opaque markers. The primary route for the excretion of chlorhexidine was through the feces (approximately 90%). The mean peak plasma level of chlorhexidine was 0.206 mc/g, reached 30 minutes after ingestion of a 300 mg dose of the drug. Chlorhexidine was not detectable in plasma 12 hours after ingestion.

Urine samples contained 0.5 to 1% of the <sup>14</sup>C-chlorhexidine gluconate administered to the study subjects.

## **TOXICOLOGY:**

### **Acute Toxicity Studies**

The oral LD<sub>50</sub> of chlorhexidine gluconate was estimated as 1.476 g/kg in rats and 0.1122 g/kg in rabbits. The oral LD<sub>50</sub> of the mouth rinse formulation was estimated at > 20 g/kg in rats.

### **Chronic and Subchronic Toxicity Studies**

The only consistently observed finding in eight subchronic and chronic toxicity studies was the accumulation of foamy macrophages in the mesenteric lymph nodes of rats. Representative samples of these lesions were evaluated by two independent pathologists. They concluded that the lesions did not represent a significant toxic effect. This conclusion is supported by the following facts: 1) The macrophages do not contain bacteria, indicating that a significant change in the intestinal flora has not occurred. 2)

The reaction is not associated with increased morbidity or mortality. 3) The reaction does not become progressively more severe with continued exposure to chlorhexidine. 4) The reaction is reversible after administration of chlorhexidine is discontinued.

### **Reproduction and Teratology**

No adverse reproductive or teratologic effects on rats or rabbits were observed in studies with the mouth rinse formulation.

The effect of chlorhexidine gluconate on various aspects of reproductive processes has been evaluated using both the rat and rabbit as a model. An apparent embryotoxic effect was observed in rabbits that received a daily 40 mg/kg dose of chlorhexidine by gavage and in rats that ingested a 300 mg/kg dose of chlorhexidine from their diet each day. These doses are about 140 and 1040 times, respectively, the estimated daily ingestion from Chlorhexidine Gluconate Mouthwash with the recommended dose.

### **Carcinogenicity**

No evidence of carcinogenicity was reported in two rat studies in which chlorhexidine was administered in their drinking water. The studies were two years in duration and delivered chlorhexidine at dose levels of up to 200 mg/kg/day.

### **Mutagenicity**

No evidence of mutagenicity was observed when chlorhexidine gluconate was evaluated by the dominant lethal assay in mice and micronucleus assay in hamsters.

Mutagenicity studies, using bacterial cell system, with or without metabolic activation, produced contradictory results, which are unexpected with drugs having antibacterial activity.

While Suessmuth et al. (1979) and Ackerman-Schmidt et al. (1982) obtained positive results, Evans et al. (1978) and Sakagami et al. (1988) found no evidence of genotoxicity for chlorhexidine. The clinical significance of these results is unclear.

### **Immediate Hypersensitivity**

A variety of regimens were used in an attempt to induce and elicit immediate hypersensitivity to chlorhexidine gluconate in guinea pigs, rabbits, rats and man. No evidence of immediate hypersensitivity was observed in any of the tests.

### **Other Studies**

The emetic dose, irritation potential, and sensitization potential have also been determined for 0.12% Chlorhexidine Gluconate Mouthwash. Chlorhexidine Gluconate Mouthwash has an emetic ED<sub>50</sub> of approximately 13.4 mL/kg (tested in dogs using the oral route of administration), is only slightly irritating to the eye (tested in rabbits), and was not irritating to the oral mucosa (tested in dogs). In addition, the mouth rinse does not induce delayed contact sensitization.

## REFERENCES

1. Grossman, E.; Reiter, G.; Sturzenberger, O.P.; De la Rosa, M.; Dickinson, T.D.; Ferretti, G.A.; Ludlam, G.E.; Meckel, A.H.: "Six-month study of the effects of a chlorhexidine mouth rinse on gingivitis in adults." J. Periodont. Res. 1986; 21 (Suppl. 16): 33-43.
2. Briner, W.W.; Grossman, E.; Buckner, R.Y.; Rebitski, G.F.; Sox, T.E.; Setser, R.E.; Ebert, M.L.: "Effect of chlorhexidine gluconate mouthrinse on plaque bacteria." J. Periodont. Res. 1986; 21 (Suppl. 16): 44-52.
3. Briner, W.W.; Grossman, E.; Buckner, R.Y.; Rebitski, G.F.; Sox, T.E.; Setser, R.E.; Ebert, M.L.: "Assessment of susceptibility of plaque bacteria to chlorhexidine after six months' oral use." J. Periodont. Res. 1986; 21 (Suppl. 16): 53-59.
4. Loe, H.; Rindom-Schiott, C.; Glavind, L.; Karring, T.: "Two years' oral use of chlorhexidine in man: I. General design and clinical effects." J. Periodont. Res. 1976: 11: 135-144.
5. Rindom Schiott, C.; Briner, W.W.; Loe, H.: "Two Years Oral Use of Chlorhexidine In Man. II. The effect on the Salivary Bacterial Flora." J. Periodont. Res. 1976: 11: 145-152.
6. Warner, V.D.; Lunch, D.M.; Kim, K.H.; Grunewald, G.L.: "Quantitative Structure – Activity Relationships for Biguanides, Carbamimidates and Bisbiguanides as Inhibitors of Streptococcus Mutans." J. Med. Chem.. 22: Issue 4, 1978, 359-66
7. Suessmuth, R.; Lingens, F.; Ackermann, B.: "Mutagenic effect of 1,1'-Hexamethylene-Bis ((5-p-Chlorophenyl)- Biguanide)." Chem-Biol. Interact.: 28 (2-3) 1979, 249-258
8. Achermann-Schmidt, B.; Suessmuth, R; Lingens F.: "Effects of 1,1'-Hexamethylene-Bis ((5-p-Chlorophenyl)- Biguanide) on the genome and on the synthesis of nucleic acid and proteins in the bacterial cells." Chem-Biol. Interact.; Vol. 40, Iss. 1, 1982. 85-96.
9. Evans, R.T.; Baker, P.J.; Coburn, R.A.; Genco, R.J.; Paigen, B.J.: "Evaluation of chlorhexidine, Tribromsalan and a limited series of alkyl bis biguanides in an in-vitro mutagenicity assay." J. Dent. Res.; 1978, 57:290
10. Peridex Oral Rinse product monograph, 3M Canada Company, Date of preparation: December 12, 2007, control number 118710