

PRODUCT MONOGRAPH

PREVORA STAGE 1

(Chlorhexidine Acetate) 10% w/v

Antimicrobial Agent

CHX Technologies Inc.
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Date of Preparation:
August 18, 2004

Product Monograph

NAME OF DRUG

Prevora Stage 1

(Chlorhexidine Acetate)

10% w/v

THERAPEUTIC CLASSIFICATION

Antimicrobial Agent

ACTION

The antimicrobial action of chlorhexidine results from its adsorption on to the cell wall of *Streptococcus mutans*, resulting in an alteration or breakdown of the structure of these bacteria.

INDICATIONS

To be used in dental offices only. Prevora Stage 1 (chlorhexidine acetate) is indicated for the reduction of root caries in adults at high risk of dental caries.

CONTRAINDICATIONS

Prevora Stage 1 (chlorhexidine acetate) is contraindicated in patients with a history of eczema or of allergies to chlorhexidine salts or Sumatra benzoin. Such allergies are rare but have been reported in the literature. Such allergies have not been reported during or after use of Prevora Stage 1.

PRECAUTIONS

Prevora Stage 1 (chlorhexidine acetate) should be used with caution in patients with a

history of asthma. Avoid application of Prevora Stage 1 or Prevora Sealant Stage 2 to the soft tissues. Failure to do so can result in temporary stinging or inflammation of the tissues.

Usage in Pregnancy: No controlled clinical trials have been carried out to ascertain if there are any adverse reactions when Prevora Stage 1 is applied to the dentition of expectant mothers. Therefore, it is recommended that Prevora Stage 1 should not be administered during pregnancy.

Usage in Nursing Mothers: Since many drugs are excreted during lactation and there have not been any studies performed using Prevora Stage 1 in nursing mothers, it is recommended that Prevora Stage 1 should not be applied if the mother is nursing.

ADVERSE REACTIONS

Chlorhexidine is known to occasionally cause a brown staining of the teeth especially when used in long-term daily mouth rinses. This staining has been infrequently reported with Prevora Stage 1 (chlorhexidine acetate) in controlled clinical trials and in Canadian dental use. Stains can be removed with a dental prophylaxis.

Immediate hypersensitivity reactions to chlorhexidine (urticaria or anaphylaxis), though rare, have been documented for other chlorhexidine formulations. These hypersensitivity reactions have not been seen in controlled clinical trials and in Canadian dental use of Prevora Stage 1.

Other minor adverse reactions include an objectionable taste associated with accidental

contact of Prevora Stage 1 with the oral mucosa; localized areas of white precipitate on the margin of the gingivae or on the teeth as a result of contact of the solution with moisture before it had set; redness and/or a burning sensation at the margin of the gingivae; excessive roughness of the solution layer to the tongue All these effects are temporary and mild.

Adverse reactions were seen in the minority of patients treated and all were attributed to lapses in technique.

SYMPTOMS AND TREATMENT OF OVERDOSE

There is no experience with over-dosage with Prevora Stage 1 (chlorhexidine acetate). Consequently, the signs and symptoms have not been identified. If overdose should occur, treat symptomatically.

DOSAGE AND ADMINISTRATION

The procedure for administration of Prevora Stage 1 (chlorhexidine acetate) and Prevora Sealant Stage 2 is described below in 12 steps.

Up to 0.600 ml of Prevora Stage 1 and then Prevora Sealant Stage 2 are consecutively applied to the full dentition of adults in a single treatment. Over the course of seven months involving 5 applications, a cumulative volume of up to 3.0 ml of Prevora Stage 1 and Prevora Sealant Stage 2 is applied to the patient's teeth.

Treatment Procedures:

1. Ensure that the dentition contains no open caries lesions or restorations with imperfect margins. Prepare for the application with a tray as shown below, consisting of cotton rolls, cotton pellets or fine brushes, a forceps, air syringe and the box of Prevora Stage 1 and Prevora Sealant Stage 2.



2. Give a rubber cup prophylaxis using flour of pumice and water, or a non-oil based prophylactic paste.



3. Thoroughly rinse and floss the patient's teeth with un-waxed floss to remove pumice and residual dental plaque. Ensure the cleanliness of the distal surface of the last tooth in each arch by wiping it with a cotton pellet held in a pair of forceps.
4. Isolate one quadrant of the dentition with cotton rolls and a saliva ejector.



5. Dry all teeth in that quadrant with an air syringe.
6. Using a cotton pellet held in forceps, or a fine brush suitable for reaching interproximal areas, apply Prevora Stage 1 to the interproximal areas of all posterior teeth in the quadrant.



7. Again dry the tooth surfaces of that quadrant with the air syringe and apply Prevora Stage 1 to all tooth surfaces; dry Prevora Stage 1 briefly with an air syringe.



8. Apply Prevora Sealant Stage 2 over the Prevora Stage 1 with a second cotton pellet or with another fine brush; dry Prevora Sealant Stage 2 with an air syringe.



9. Repeat steps 4 through 8 on each of the other quadrants.
10. Advise the patient: (i) that the dried Prevora film will begin coming off the teeth during the next meal; (ii) to avoid eating hard foods for at least 4 hours after treatment; (iii) to avoid tooth-brushing for 24 hours after treatment and then to resume tooth-brushing with a new brush; (iv) not to chew gum for 24 hours, and; (v) to avoid flossing for 3 days.
11. Instruct the patient to control sugar intake and to follow regular oral hygiene practices, including brushing with a fluoridated dentifrice and frequent flossing. Provide the patient with the Information for the Patient leaflet which further explains this treatment and the important procedures to be followed after treatment.
12. Repeat this initial Prevora application every week for 3 more weeks after the initial application, followed by a single application at six months and thereafter according to professional judgement. The patient should be followed-up for an assessment of caries risk and experience between 3 and 6 months thereafter, according to standard recall procedures for patients at risk of dental caries.

Instruments, clothing etc. in contact with Prevora Stage 1 may be cleaned with alcohol.

PHARMACEUTICAL INFORMATION

(i) Drug substance

The active ingredient in Prevora Stage 1 is chlorhexidine acetate.

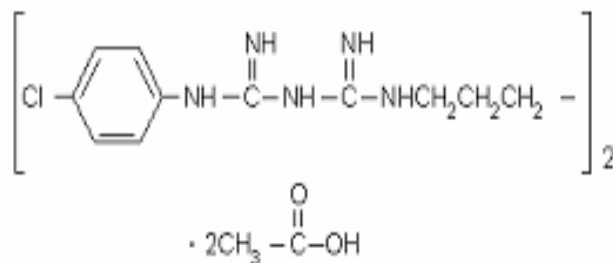
Chemical Name:

1,1' – hexamethylenebis (5 – [4-chlorophenyl] biguanide) diacetate

Molecular Formula:



Structural Formula:



Molecular Weight:

625.6 a.m.u.

Description:

Chlorhexidine acetate is a white crystalline powder. It is soluble in 55 parts of water and in 15 parts of 96% ethanol.

(ii) Composition

Prevora Stage 1

<u>Ingredient</u>	<u>Grams per 100mL of Prevora Stage 1</u>
Chlorhexidine acetate BP	10
Sumatra benzoin USP	20
dissolved in absolute ethyl alcohol USP	qs

(iii) Stability and Storage Recommendations

Prevora Stage 1 (chlorhexidine acetate) is packaged in light-resistant amber glass vials. Prevora Stage 1 is to be stored in a refrigerator at between 2 and 8 degrees Celsius. Prevora Stage 1 may become darker in color with time. This is expected and does not affect the shelf life.

DOSAGE FORMS

Availability

Prevora Stage 1 (chlorhexidine acetate) is packaged in 1 mL aliquots in 2 mL glass vials at a strength of 10% w/v chlorhexidine acetate.

Prevora Stage 1 along with Prevora Sealant Stage 2 (one treatment set) is packaged in a box containing 6 treatment sets or 12 glass vials.

INFORMATION FOR THE PATIENT

PREVORA STAGE 1 (CHLORHEXIDINE ACETATE)

Read all of this leaflet carefully regarding your treatment with the Prevora Stage 1 dental coating in your dentist's office. Keep this leaflet for future reference. If you have further questions, please ask your dental professional. This medicine has been prescribed for you and will be applied to your teeth by your dental professional on several occasions.

In this leaflet:

1. What Prevora Stage 1 is and what it is used for.
2. Before you are treated with Prevora Stage 1.
3. How you are treated with Prevora Stage 1.
4. Possible side effects.
5. What to do after you are treated with Prevora Stage 1.
6. Further information.

1. WHAT PREVORA STAGE 1 IS AND WHAT IT IS USED FOR:

Prevora Stage 1 dental coating is a topical oral treatment for tooth decay occurring at the root surfaces. This coating temporarily covers your teeth to reduce the bacteria on your teeth which cause tooth decay.

The active substance in Prevora Stage 1 is chlorhexidine.

The other ingredients in Prevora Stage 1 are Sumatra benzoin and absolute ethyl alcohol.

2. BEFORE YOU ARE TREATED WITH PREVORA STAGE 1:

You should not be treated with Prevora Stage 1:

If you are allergic to chlorhexidine, Sumatra benzoin or ethyl alcohol.

If you are allergic to the ingredients of Prevora Sealant Stage 2, which is a secondary coating applied immediately over Prevora Stage 1. The ingredients of this second coating are methacrylate, triethyl citrate and purified water.

Take special care before undergoing treatment with Prevora Stage 1 to report any medical condition, including asthma, eczema and other allergies, to your dentist.

Pregnancy: Ask your dentist for advice before taking or receiving any medicine.

Breast-feeding: Ask your dentist for advice before taking or receiving any medicine.

Driving and using machines: Prevora Stage 1 has not been shown to affect driving or the use of machines.

Important information about some of the ingredients of Prevora Stage 1: This dental coating can cause a temporary irritation or stinging of the gums, lips or tongue and can also have a bitter taste.

Taking other medications: Please inform your dental professional if you are taking or have recently taken any other medications, even those not prescribed.

3. HOW YOU ARE TREATED WITH PREVORA STAGE 1:

This topical, temporary coating on your teeth is applied by your dental professional in a short appointment in the dental office. The dental professional will first clean your teeth, and then apply Prevora Stage 1 to all tooth surfaces as pictured below, followed immediately by a second coating of Prevora Sealant Stage 2. This second coating temporarily protects Prevora Stage 1 from your saliva and from food abrasion.



At the start of your treatment with Prevora Stage 1, you will require 4 weekly treatments followed by another single treatment in six months. Thereafter, your need for more treatments with Prevora Stage 1 will be evaluated by your dental professional.

Effects when the Prevora treatment is finished: Temporarily, you may have a bitter taste, a sensation of a coating on your teeth and/or a stinging or burning along your gum line or tongue. The bitter taste and stinging will likely last for a few minutes, the coating for a few hours.

4. POSSIBLE SIDE EFFECTS:

If you have prolonged stinging or burning of the gums, lips or tongue, you should contact your dental professional as soon as possible.

If you notice any side effects not mentioned in this leaflet, please inform your dental professional.

5. WHAT TO DO AFTER YOU ARE TREATED WITH PREVORA STAGE 1:

To preserve this coating on your teeth for as long as possible, eat soft foods at your next meal (e.g. soup). Do not eat hard foods (e.g. meat, apples) for at least 4 hours after treatment.

Do not chew gum for at least 24 hours.

Do not brush your teeth for 24 hours after this treatment. Then begin brushing with a new tooth brush and brush 2 to 3 times daily with fluoride toothpaste.

Do not floss your teeth for 3 days following this treatment. Then resume flossing daily.

If dentures are worn, clean and disinfect at home prior to use. Disinfect using soap and warm water.

Make sure you receive all the treatments of Prevora Stage 1, as prescribed by your dentist.

It is important to the overall success of this treatment that you regularly brush your teeth with a fluoridated tooth paste, and that you control your consumption of foods and drinks which have a high amount of sugar.

6. FURTHER INFORMATION:

For any information about this dental coating, contact:

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D.I.N. #02046245 as of September 2004.

MICROBIOLOGY

It has been shown *in vitro* that *Streptococcus mutans* are highly susceptible to chlorhexidine acetate. The minimum inhibitory concentration of 11 strains of *Streptococcus mutans* to chlorhexidine acetate is between 0.39 and 1.56 micrograms per mL.

Prevora Stage 1 (chlorhexidine acetate), assessed *in vitro* in buffer which was changed daily, released an initial burst of about 1.2 mg of chlorhexidine in the first 24 hours, followed by a 10 day period in which the rate of release was approximately constant (zero order kinetics). The concentration of chlorhexidine attained daily in each sample of the buffer solution remained above 10 ug/mL, which was determined to be above the minimum bactericidal concentration for several strains of *Streptococcus mutans* (M.B.C. less than 6.25 ug/mL).

There has been no evidence of an alteration in the balance of the other oral microflora or of any detectable increases in gingivitis index in association with treatment with Prevora Stage 1.

CLINICAL STUDIES

In a multi-centered, randomized, placebo-controlled, double-blinded study involving 240 patients, average age of 58.7 years, with medication-induced xerostomia (average unstimulated salivary flow of 0.2 ml/min.), Prevora Stage 1 (chlorhexidine acetate) significantly reduced the increment of root caries over a 12 month period of observation.

Table 1 Reduction in Caries Increment in the Trial of 240 Medication-induced Xerostomic Adults
- one year period of treatment and observation and 5 treatments –

group	Caries increment	% reduction active vs. placebo	P value active vs. placebo (two sided, LOCF)
Prevora Stage 1 coronal surfaces	1.79	14.4%	0.0644
Placebo coronal	2.09		
Prevora Stage 1 root surfaces	0.77	40.8%	0.0206
Placebo root	1.30		

Five applications of Prevora Stage 1 were administered during this study, including four weekly applications in the first month and a single application at month six. The dose per application was between 300 µl and 600 µl of chlorhexidine.

In this study, there were no serious adverse events related to the application of Prevora Stage 1. Adverse events related to Prevora Stage 1 were generally mild, limited to the oral cavity and involved abnormal taste, stinging and burning of the oral mucosa and temporary loss of taste acuity.

PHARMACOLOGY

No pharmacology data are available for Prevora Stage 1 (chlorhexidine acetate).

However, chlorhexidine digluconate has been studied extensively. A metabolic study was conducted using radiolabelled chlorhexidine digluconate. Animals and one human volunteer were dosed orally. The results of these studies are summarized as follows:

- Chlorhexidine is a poorly absorbed drug. In the human volunteer, no chlorhexidine was detected in the blood after the oral administration of 0.07 mg of chlorhexidine per kilogram of body weight.
- The small amount that is absorbed initially is metabolized by the liver and the kidney.
- Chlorhexidine has an affinity for mucosal surfaces in the alimentary tract, including the mouth.
- Circulating blood levels following oral dosing to dogs are extremely low.
- Detectable amounts of p-chloroaniline are not produced from the enzymatic metabolism of the chlorhexidine.

TOXICOLOGY

Animal Studies: The acute oral toxicity of chlorhexidine is low, with an LD₅₀ of chlorhexidine acetate in mice of 2000 mg/kg. Chlorhexidine is poorly absorbed by the gastro-intestinal tract and almost entirely excreted in the faeces. In an acute and long-term toxicity study involving rats, the Prevora Stage 1 (chlorhexidine acetate) and its ingredients administered at 150 µl per day over 14 days to the dentition and oral mucosa, resulted in no systemic or local drug/treatment related toxicity.

Human Studies: The single dose of chlorhexidine acetate administered to adults in one treatment of Prevora Stage 1 ranges between 30 mg and 60 mg depending on the size of the mouth and number of teeth of the patient.

The maximum daily dose based on 1.0 mL of 10% w/v chlorhexidine acetate in Prevora Stage 1 would be 100 mg of chlorhexidine acetate. The total dose per week would be the same as the daily dose of 100 mg, while the total dose after 4 weeks of treatment would be 400 mg. These doses are well below the level of 2,000 mg per day that adults have shown to be able to consume for a week without adverse effects.

Long-term oral use in the form of a daily chlorhexidine mouthwash by humans has not produced changes in hematological and biochemical parameters. However, oral intolerances such as desquamation or ulceration of the oral mucosa have occurred after use of chlorhexidine mouth rinses. It has been reported that exposure of human cells in culture to chlorhexidine in equal to or greater than 0.004% resulted in impaired cellular function and/or cell death.

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