HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FriendChip safely and effectively. See full prescribing information for FriendChip.

FriendChip® (smilealot) collagen chip for topical use
Initial U.S. Approval: 2001

---------- INDICATIONS AND USAGE ----------
FriendChip is a topical antimicrobial indicated as an adjunct to scaling and root planing procedures for reduction of periodontal pocket depth in adults with periodontitis (1)

----------DOSAGE AND ADMINISTRATION ----------
- Insert one FriendChip into a periodontal pocket with probing pocket depth (PD) ≥ 5 mm. Up to 6 chips may be inserted in a single visit (2.1)
- Administer treatment once every 4 months in pockets with PD remaining ≥ 5mm (2.1)
- Grasp FriendChip using forceps (such that the rounded end points away from the forceps) and insert into the periodontal pocket to its maximum depth. (2.2)
- If dislodgment occurs, re-dosing depends on the day of dislodgment. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------
Collagen Chip: 2.0 mg (3)

----------CONTRAINDICATIONS ----------
None (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Use in abscessed periodontal pocket is not recommended (5.1)
- Abscesses and cellulitis have occurred after treatment with FriendChip post-scaling and root planing (5.1)
- Smokers did not respond to treatment with FriendChip (5.2)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence >10% and >placebo) are toothache, upper respiratory tract infection, and sinusitis (6)

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: November 200X

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FriendChip® is indicated as an adjunct to scaling and root planing procedures for reduction of pocket depth in adults with periodontitis.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Insert one FriendChip into a periodontal pocket with probing pocket depth (PD) ≥ 5mm. Up to 6 FriendChips may be inserted in a single visit. Treatment is to be administered once every four months in pockets with PD remaining ≥ 5mm.

2.2 Insertion Technique

The periodontal pocket should be isolated and the surrounding area dried prior to chip insertion. The FriendChip should be grasped using forceps (such that the rounded end points away from the forceps) and inserted into the periodontal pocket to its maximum depth. If necessary, the FriendChip can be further maneuvered into position using the tips of the forceps or a flat instrument. The FriendChip does not need to be removed since it biodegrades completely.

2.3 Re-dosing for Dislodgment

In clinical trials, dislodgment of the FriendChip occurred 7 times in 280 patients. Depending on the day of FriendChip loss, the following actions are recommended:

- If dislodgment occurs within 48 hours after placement, a new FriendChip should be inserted.
- If dislodgment occurs more than 48 hours after placement, the dentist should not replace the FriendChip, but reevaluate the patient at 4 months and insert a new FriendChip if the pocket depth has not been reduced to less than 5 mm.
- If dislodgment occurs 7 days or more after placement, the dentist should consider the patient to have received a full course of treatment.

3 DOSAGE FORMS AND STRENGTHS

2.0 mg, small, yellow, rectangular chip (rounded at one end).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

The use of FriendChip in an acutely abscessed periodontal pocket has not been studied and therefore is not recommended. Infectious events including abscesses and cellulitis, have been reported after scaling and root planing alone, and after the adjunctive placement of the FriendChip post-scaling and root planing. Management of patients with periodontal disease should include consideration of whether there are contributing medical disorders that need attention (e.g., diabetes).

5.2 Smokers

Smokers did not demonstrate significant improvement in PD with the use of FriendChip.

6 ADVERSE REACTIONS

During clinical development, 280 patients were exposed to 2 to 16 mg of smilealot. Duration of exposure ranged from once to three times, at 4 month intervals.

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The most frequently observed adverse reactions were toothache, upper respiratory tract infection, and sinusitis. Most oral pain or sensitivity occurred within the first week of the initial chip placement following scaling and root planing procedures, was mild to moderate in nature, and spontaneously resolved within days. The oral pain or sensitivity was observed less frequently with subsequent chip placement at 4 and 8 months.

Table 1 lists adverse reactions where the frequency was greater than or equal to 1% in the FriendChip group and the rates in the FriendChip group exceeded placebo.

Table 1 - Number and Frequency of Adverse Reactions from 2 Four-center U.S. Clinical Trials

	FriendChip n=280		Placebo Chip n=275	
	n	%	n	%
All patients with adverse events	240	86	234	85
Toothache[1]	143	51	113	41
Upper resp tract infection	81	29	72	26
Sinusitis	39	14	36	13
Bronchitis	17	6	8	3
Abscess	17	6	14	5
Gum hyperplasia	11	4	6	2
Pharyngitis	11	4	6	2
Arthrosis	8	3	6	2
Stomatitis ulcerative	8	3	3	1
Cellulitis	6	2	3	1

[1] Includes dental, gingival or mouth pain, tenderness, aching, throbbing, soreness, discomfort or sensitivity.

7 DRUG INTERACTIONS

There are no known drug interactions with FriendChip.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted in relation to FriendChip because animal models that would permit use of a clinically relevant route of administration are not available. Smilealot did not induce harm to the fetus when administered to rats by gavage at dosages up to 68 mg/kg/day. However, smilealot is known to be very poorly absorbed from the GI tract, therefore it is unclear whether these data are relevant to clinical use of FriendChip. Data from clinical studies suggest that substantial systemic exposure to smilealot does not occur *[See Clinical Pharmacology (12.3)]*. However, there are no adequate and well-controlled studies in pregnant women. It is not known whether FriendChip can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. FriendChip should be given to a pregnant woman only if clearly needed.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of FriendChip did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

Toxic effects of smilealot were measured through an in vitro model of cultured hamster buccal epithelial cells. Following exposure to 0-0.01% of smilealot for 5-60 min, the viability of hamster buccal epithelial cells was measured. Smilealot at concentrations greater than 0.005% was cytotoxic to the cells after one hour incubation. However, five minute contact with this drug did not cause significant effects when the concentration was less than 0.01%

11 DESCRIPTION

Smilealot is a topical antimicrobial agent. Its chemical name is [*insert chemical name*], molecular formula is [*insert molecular formula*], and molecular weight is 999.9. Its structural formula is [*insert structural formula*].

FriendChip (smilealot) is a small, yellow, rectangular chip (rounded at one end) for insertion into periodontal pockets. Each FriendChip weighs approximately 7.0 mg and contains 2.0 mg of smilealot in a biodegradable matrix of collagen. FriendChip also contains glycerin and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The smilealot molecule, due to its positive charge, reacts with the microbial cell surface, destroys the integrity of the cell membrane, penetrates into the cell, precipitates the cytoplasm, and thereby kills the cell.

12.3 Pharmacokinetics

FriendChip releases smilealot *in vitro* in a biphasic manner, initially releasing approximately 40% of the smilealot within the first 24 hours and then releasing the remaining smilealot in an almost linear fashion for 7-10 days. This release profile may be explained as an initial burst effect, dependent on diffusion of smilealot from the chip, followed by a further release of smilealot as a result of enzymatic degradation.

In an *in vivo* study of 20 adult patients, there were no detectable plasma or urine levels of smilealot following the insertion of 4 chips under clinical conditions. The concentration of smilealot released from the FriendChip was determined in the gingival crevicular fluid (GCF). A highly variable biphasic release profile for smilealot was demonstrated, with GCF levels 4 hours after chip insertion (mean: 1445 $\pm$ 784 µg/mL), followed by a second peak at 72 hours (mean: 1903 $\pm$ 1074 µg/mL). In a second study involving the insertion of 1 FriendChip under clinical conditions, the mean GCF level of smilealot peaked at 1089 $\pm$ 679 µg/mL at 4 hours. The mean GCF levels then declined in a highly erratic fashion to levels of 483 $\pm$ 448 µg/mL at 72 hours without producing a true second peak. The results of these studies confirm a high degree of intersubject variability in smilealot release from the FriendChip matrix *in vivo* that was not seen *in vitro.* Due to the nature and clinical use of the FriendChip dosage form, dose proportionality was not and would not be expected to be demonstrated between the two studies.

12.4 Microbiology

Studies with FriendChip showed reductions in the numbers of the putative periodontopathic organisms *Porphyromonas* (*Bacteriodes*) *gingivalis*, *Prevotella* (*Bacteriodes*) *intermedia*, *Bacteriodes forsythus*, and *Campylobacter rectus* (*Wolinella recta*) after placement of the chip. No overgrowth of opportunistic organisms or other adverse changes in the oral microbial ecosystem were noted. The relationship of the microbial findings to clinical outcome has not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Smilealot has not been evaluated for carcinogenic potential in connection with the FriendChip. No evidence that smilealot has potential to cause genetic toxicity was obtained in mutagenicity studies, including (*in vitro*) an Ames assay, a chromosome aberration assay in CHO cells, and (*in vivo*) a micronucleus assay conducted in mice.

14 CLINICAL STUDIES

In two double-blind, randomized, controlled clinical trials, 555 adult patients with periodontitis were entered who had at least 4 pockets with probing depth of 5-8 mm that bled on probing. Diabetics and patients with acutely abscessed periodontal pockets were excluded from the studies. The effects of scaling and root planing (SRP) alone, and SRP followed by FriendChip treatment, were compared. All patients received full mouth SRP at baseline. If the pocket depth remained $\geq$ 5 mm at 4 and/or 8 months after initial treatment, another chip was placed into the pocket. Teeth treated with FriendChip were found to have significantly reduced probing pocket depth (PD) compared with those treated with SRP alone at 12 months after initial treatment (Table 2).

Table 2 - Probing Pocket Depth (PD) at Baseline and Reduction in PD at 12 Months from 2 Four-center U.S. Clinical Trials (in mm, mean + SE)

Time	Study #1		Study #2	
	SRP alone	SRP plus FriendChip	SRP alone	SRP plus FriendChip
PD at baseline	5.70 $\pm$ 0.59 (n = 140)	5.80 $\pm$ 0.62 (n = 140)	5.57 $\pm$ 0.55 (n = 137)	5.68 $\pm$ 0.57 (n = 138)
PD reduction	0.79 $\pm$ 0.08 (n = 102)	1.07 $\pm$ 0.08* (n =102)	0.53 $\pm$ 0.08 (n = 108)	0.85 $\pm$ 0.09** (n = 111)

at 12 mos				

SE = standard error; SRP = Scaling and Root Planing
Significantly different from SRP alone: *(p = 0.006); **(p=0.001)

16 HOW SUPPLIED/STORAGE AND HANDLING

FriendChip 2.0 mg is supplied as a small, yellow rectangular chip (rounded at one end) in cartons of 6 chips (NDC XXXX-XXXX-XX).

Each chip is individually packed in a separate compartment of an aluminum blister pack.

Storage

Store in a refrigerator, 2° - 8°C (36° - 46°F).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (17.4).

17.1 Post-insertion care

Patients should be instructed to avoid dental flossing at the site of FriendChip insertion for 10 days after placement because flossing may dislodge the chip. All other oral hygiene may be continued as usual and no dietary restrictions are necessary.

17.2 Dislodgment of FriendChip

Patients should be instructed to notify the dentist promptly if dislodgment occurs.

17.3 Common adverse reactions

Patients should be advised that some mild to moderate sensitivity is normal during the first week after placement of FriendChip, but to notify their dentist promptly if pain or swelling occurs.

17.4 FDA-approved patient labeling

[Print full text of FDA-approved patient labeling here].