

Labelling – Indications/Warnings

5.C. Revisions to the labeling in the ANPR-recommended labeling of OTC Antigingivitis/Antiplaque Products are needed

Procter & Gamble have reviewed the proposed labeling and are recommending modifications to the proposed indications and warnings. The **indications** sections should be revised in order that basic antigingivitis labeling is consistent for all products and the indications broadened to allow multiple descriptions of drug action. Addition of a few words for technical clarification into the regulations will achieve this goal. The proposed **warnings** in the panel report should be revised and the intent incorporated into a revised warning and the directions section of the label. To address these concerns, we recommend inclusion of the phrase "See your dentist regularly," under the Other information and revised language under the Warnings section to incorporate consultation of a dentist if the condition persists or worsens.

5.C.1. The Indications and Uses Should Be Revised

"Indications" on OTC labels are synonymous with the term "uses." Indications are differentiated from the Statement of Identity by location and content. Indications usually expand on the type of benefits that can be expected from the product. The Plaque Subcommittee recommendations are very restrictive in the types of information that can be conveyed to the consumer in the "uses" section of the Information Panel. No provisions were made for the multiple effects of the antigingivitis agent by the Subcommittee. The Plaque Subcommittee recommended "Uses" for antigingivitis and antigingivitis/antiplaque products are summarized in the following table.

The Plaque Subcommittee Recommended Indications			
356.65 (b)(1): For all antigingivitis products.	356.65 (b)(2): For antigingivitis products containing stannous fluoride	356.65 (b)(3): For all antigingivitis/antiplaque products.	356.66 (b)(10:) For permitted combinations
helps [select one of the following]: <ul style="list-style-type: none"> • Control • Reduce • Prevent 	helps interfere with harmful effects of plaque associated with gingivitis	helps [select one of the following]: <ul style="list-style-type: none"> • Control • Reduce • Prevent • Remove 	One or more of the indications for antigingivitis/antiplaque active ingredients or the following: <ul style="list-style-type: none"> • helps [select one of the following]: <ul style="list-style-type: none"> ▪ Control ▪ Inhibit ▪ Kill
select one or more of the following: <ul style="list-style-type: none"> • Gingivitis • Gingivitis, an early form of gum disease • Bleeding gums 		plaque that leads to [select one or more of the following]: <ul style="list-style-type: none"> • Gingivitis • Gingivitis, an early form of gum disease • Bleeding gums 	plaque bacteria that contribute to the development of [select one or more of the following]: <ul style="list-style-type: none"> • Gingivitis • Gingivitis, an early form of gum disease • Bleeding gums

5.C.1.1. Indications and Uses Should be Broadened to Allow Multiple Descriptions of Drug Action

The ANPR has recommended that only one word from among “control, reduce or prevent” gingivitis, gingivitis - an early form of gum disease, or bleeding gums be permitted to describe the benefit of the product. This recommendation is very restrictive in the information that can be conveyed to the consumer in the “uses” section of the Information Panel because the terms “control, reduce or prevent” are not mutually exclusive. It is highly possible that a consumer with mild gingivitis would purchase a product to control or reduce their gingivitis and continue to use the same product in an attempt to prevent future gingivitis. Such a product should be labeled for both indications if it is entirely the same product with more than one use.

Procter & Gamble is in generally agreement with the CHPA/CTFA Industry Task Group recommendation that for antigingivitis (356.65 (b)(1), antigingivitis/antiplaque (356.65 (b)(3) and combination products covered by (356.66(b)(10) products, use of one or more of the statements (control, reduces, prevents) should be allowed as these statements are not mutually exclusive and can provide consumers with truthful information about the product. In addition, based on the new data supporting plaque reduction in this submission, P&G recommends that SnF₂ have the same plaque claims as included in 356.65 (b)(3). An example of Drug Facts labeling illustrating these recommendations is located in section 5.C.3. The indications should be revised to read as follows:

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Summary of Recommendations* for Labeling "Uses"

356.65 (b)(1) For all antigingivitis products	356.65(b)(2) For antigingivitis products containing stannous fluoride		356.65(b)(3) For all antigingivitis/antiplaque products		
helps [select one <u>or more</u> of the following] • control • reduce • prevent [Select one or more of the following] • gingivitis • gingivitis, an early form of gum disease • bleeding gums	helps [select one <u>or more</u> of the following] • control • reduce • prevent [Select one or more of the following] • gingivitis • gingivitis, an early form of gum disease • bleeding gums		helps [select one <u>or more</u> of the following] • control • reduce • prevent [Select one or more of the following] • <u>gingivitis</u> • <u>gingivitis, an early form of gum disease</u> • <u>bleeding gums</u>		
AND <u>helps interfere with the harmful effects of plaque</u> or <u>helps</u> [select one <u>or more</u> of the following] • <u>control</u> • <u>reduce</u> • <u>prevent</u> • <u>remove</u> <u>plaque</u>		OR helps interfere with the harmful effects of plaque associated with [Select one or more of the following] • gingivitis • <u>gingivitis, an early form of gum disease</u> • <u>bleeding gums</u>	AND <u>helps</u> [select one <u>or more</u> of the following] • <u>control</u> • <u>reduce</u> • <u>prevent</u> • <u>remove</u> <u>plaque</u> OR Helps [select one <u>or more</u> of the following] • control • reduce • prevent • remove plaque that leads to [select one or more of the following] • gingivitis • gingivitis, an early form of gum disease • bleeding gums		
					AND (OPTIONALLY) <u>helps</u> [select one <u>or more</u> of the following] • <u>control</u> • <u>inhibit</u> • <u>kill</u> <u>plaque bacteria</u>

* Additions are **bolded**, underlined and *italicized*

5.C.2. The warning specified for all Category I active ingredients is inappropriate and is inconsistent with labeling for an NDA-approved OTC gingivitis product. All products should include a statement regarding the need for regular dental checkups in the "Other information" section of the labeling. Antigingivitis products labeled for treatment or control of gingivitis should include a warning to "Ask a dentist if the condition persists or worsens after regular use."

The warning language proposed by the Plaque Subcommittee should not be included in the monograph; however, the intent of the warning could be incorporated into a revised warning and the other information where it provides more useful direction to consumers in the OTC label format. The proposed warning is inconsistent with longstanding FDA policy on warnings. The language contains information that would be misleading to consumers by not conveying appropriate use information, delaying needed professional treatment and discontinuation of a product that may in fact be helpful to a consumer.

FDA has repeatedly stated that warnings should only contain essential information necessary to assure the proper and safe use of the OTC drug product by the consumer.⁷² This is consistent with the statutory requirement under the FD&C Act to disclose "material" facts about product use. Thus, FDA does not support warnings for every possible and/or theoretical hazard that might be encountered during OTC use. Instead, FDA requires that warnings are to be data-driven, in the context of its longstanding policy for OTC warnings, which states that OTC warnings should be "scientifically documented, clinically significant, and important to the safe and effective use of the product by the consumer."⁷³ Continued application of the

⁷² 48 *Fed Reg.* 1983 at 6830; 53 *Fed Reg.* 1988 at 2455; 57 *Fed Reg.* 1994 at 58369; 59 *Fed Reg.* 1994 at 43386,43399.

⁷³ 53 *Fed Reg.* 1988: 46204-260 and 47 *Fed Reg.* 1992: 54754.

Agency's OTC warning policy should remain a high priority for FDA, as it is the right approach for creating meaningful labeling safeguards for consumers.

The Plaque Subcommittee has recommended the following warning for all antigingivitis and antigingivitis/antiplaque products:

“Stop use and ask a dentist if

- gingivitis, bleeding, or redness persists more than 2 weeks
- you have painful or swollen gums, pus from the gum line, loose teeth, or increasing spacing between the teeth. These may be signs or symptoms of periodontitis, a serious form of gum disease.

The warning recommended by the Subcommittee is inappropriate because:

- it does not take into account the fact that gingivitis symptoms often take longer than 2 weeks to subside,
- consumers should not stop their gingivitis medication before going to the dentist, as lack of any antigingivitis therapy may exacerbate the condition further, and
- many of the symptoms listed in the warning are severe periodontitis symptoms (e.g. pus from gum line, loose teeth or increasing spacing between teeth). It would be inappropriate to delay seeing a dentist until the time that severe periodontitis symptoms occur.

Since the indications for antigingivitis and antigingivitis/antiplaque active ingredients include wording to use the product either as a treatment for gingivitis, or to prevent gingivitis, the information on how to use the product should provide options that take these two types of uses into account. These options would provide more appropriate labeling language for each option than using the single warning recommended by the Subcommittee for all uses.

For all products (whether for prevention or treatment), the statement “See your dentist regularly” should be placed in the “Other information” section of labeling. This will ensure that consumers understand that the OTC product is not a replacement for regular dental check-ups.

For products that are labeled for prevention of gingivitis, there is no need to provide a “stop use” or “when using this product” warning because the product will be used by consumers with healthy gums to aid in the prevention of plaque and gingivitis. Deletion of this warning would be consistent with the Agency’s NDA-approved labeling for Colgate Total[®] Toothpaste which is indicated for prevention of caries, plaque and gingivitis.

For products that are labeled for treatment of gingivitis, e.g. “control,” or “reduce” gingivitis, or “control,” “reduce,” or “remove” plaque that leads to gingivitis, the following label statement should be provided in the “Warnings” section of the labeling: “Ask a dentist if the condition persists or worsens after regular use.” This warning properly instructs the consumer to see the dental professional if gingivitis is getting worse, and ensures that the consumer does not stop using the product which could cause precipitous exacerbation of the disease process.

We believe the recommendations above provide meaningful labeling information to the consumer regarding how to use the antigingivitis/antiplaque product and when to seek the advice of a dental professional. This type of labeling will better meet the needs of consumers to assure the safe and effective use of the product.

5.C.3. Drug Facts Labeling – Summarized

For All Antigingivitis/Antiplaque Products That “Control” or “Reduce”

To address these concerns, P&G recommends inclusion of revised language under the warnings section that incorporates consultation with a dentist if the condition does not improve and the addition of the phrase “See your dentist regularly,” under the other information section of Drug Facts. An example of a label appears below, with recommended language underlined.

<p><i>Warnings</i> <u>Ask a dentist if</u></p> <ul style="list-style-type: none">• <u>condition persists or worsens after regular use</u> <p>Keep out of reach of children under 6 years of age. If more than used for (“brushing” or “rinsing”) is accidentally swallowed, get medical help or contact a Poison Control Center right away.</p>
<p><i>Directions</i></p> <ul style="list-style-type: none">• adults and children 12 years of age and older: vigorously swish 20 milliliters of rinse between your teeth twice a day for 30 seconds and then spit out. Do not swallow the rinse.• children 6 years to under 12 years of age: supervise use• children under 6 years of age: do not use
<p><i>Other Information</i></p> <ul style="list-style-type: none">• This rinse is not intended to replace brushing or flossing• <u>See your dentist regularly</u>

For All Antigingivitis/Antiplaque Products That “Prevent”

For antiplaque/antigingivitis products indicated only for prevention, the warning statement about consultation with a dentist if the condition does not improve is not necessary. Clearly, for a prevention only product, the condition in question does not exist. Nevertheless, in this case as well, the Task Group recommends inclusion of the phrase “See your dentist regularly” under the other information section of the Drug Facts box.

Other Information

- This rinse is not intended to replace brushing or flossing.
- See your dentist regularly.

Drug Facts Labeling for Antigingivitis/Antiplaque Prevention Products

Cetylpyridinium Chloride Mouthrinse Example -- Prevention

<i>Drug Facts</i>	
<i>Active ingredient</i> Cetylpyridinium chloride (0.05%).....	<i>Purposes</i> Antigingivitis Antiplaque
<i>Uses</i>	
<ul style="list-style-type: none"> • helps prevent gingivitis • helps prevent plaque that leads to gingivitis • helps control plaque bacteria that contribute to the development of gingivitis 	
<i>Warnings</i>	
<p>Keep out of reach of children under 6 years of age. If more than used for rinsing is accidentally swallowed, get medical help or contact a Poison Control Center right away.</p>	
<i>Directions</i>	
<ul style="list-style-type: none"> • adults and children 12 yrs. & older: vigorously swish 20 milliliters of rinse between your teeth twice a day for 30 seconds and then spit out. Do not swallow the rinse. • children 6 years to under 12 years of age: supervise use • children under 6 yrs of age: do not use 	
<i>Other information</i>	
<ul style="list-style-type: none"> • this rinse is not intended to replace brushing or flossing • see your dentist regularly 	
<i>Inactive ingredients</i>	
<i>Questions [or comments]?</i> ☎ [phone symbol optional] 1-800-XXX-XXXX	

Stannous Fluoride Dentifrice Example -- Prevention

Drug Facts	
Active ingredient Stannous fluoride 0.454% (0.15% w/v fluoride ion).....	Purposes Anticavity toothpaste Antigingivitis Anti plaque
Uses • aids in the prevention of dental cavities <ul style="list-style-type: none"> • helps prevent gingivitis • helps prevent plaque that leads to gingivitis • helps interfere with the harmful effects of plaque associated with gingivitis • helps control plaque bacteria that contribute to the development of gingivitis 	
Warnings Keep out of reach of children. If more than used for brushing is accidentally swallowed, get medical help or contact a Poison Control Center right away.	
Directions <ul style="list-style-type: none"> • adults and children 2 years of age and older: brush teeth thoroughly, preferably after each meal or at least twice a day, or as directed by a dentist or doctor • instruct children under age 6 years of age in good brushing and rinsing habits (to minimize swallowing) • supervise children as necessary until capable of using without supervision • children under 2 yrs of age: ask a dentist or doctor • do not swallow 	
Other information <ul style="list-style-type: none"> • products containing stannous fluoride may produce surface staining of the teeth • adequate toothbrushing may prevent these stains which are not harmful or permanent and may be removed by your dentist • see your dentist regularly 	
Inactive ingredients	
Questions [or comments]? ☎ [phone symbol optional] 1-800-XXX-XXXX	

P&G encourages the Agency to propose alternative labeling requirements for OTC antigingivitis/antiplaque drug products (especially combination products) to comply with the requirements of the OTC drug labeling regulation.

Currently marketed Category I antigingivitis/antiplaque OTC drug products have a long and safe history of appropriate use by consumers. These products are used on a daily basis as they provide important therapeutic and often cosmetic benefits to the consumer. Antigingivitis/antiplaque products are part of a daily routine of good oral

hygiene and may be marketed in small packages to permit easy use by today's highly mobile population. As the Agency has indicated, it will "consider appropriate exemptions in their respective monographs and drug marketing applications to the extent possible."⁷⁴ P&G recommends that the Agency provide reduced labeling in order to comply with the requirements of the OTC drug labeling regulation for these products. Further, we also recommend that the Agency include these products in its definition of "convenience size"⁷⁵ and to work with industry to develop reduced labeling for these products.

⁷⁴ 64 Fed. Reg. at 13270

⁷⁵ Comments of CTFA and CHPA, July 3, 2002 to Docket Nos. 98N-0337, 96N-0420, 95N-0259 and 90P-0201