U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug Administration

Final Administrative Order (OTC000034)

Over-the-Counter Monograph M021: Anticaries Drug Products for Over-the-Counter Human Use (Posted May 2, 2023)

I. Summary

Over-the-Counter Monograph M021: Anticaries Drug Products for Over-the-Counter Human Use, as set forth in this document, is a final administrative order (final order) deemed by section 505G(b)(8) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355h(b)(8)), and effective upon enactment of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), Public Law 116-136, on March 27, 2020.

II. Background

The CARES Act added section 505G of the FD&C Act, which revised the framework for the regulation of over-the-counter (OTC) monograph drug products. Among other things, section 505G of the FD&C Act provides as a baseline status that, as of the date of enactment of the CARES Act, drugs that satisfy certain requirements described in section 505G(a)(1) or (2) are deemed to be generally recognized as safe and effective under section 201(p)(1) of the FD&C Act (21 U.S.C. 321(p)(1)), not a new drug under section 201(p), and not subject to section 503(b)(1) of the FD&C Act (21 U.S.C. 353(b)(1)). To obtain this status, among other things, a drug either must be one that is in conformity with the requirements for nonprescription use of a final monograph issued under part 330 (21 CFR part 330) (except as provided in section 505G(a)(2)),[1] as well as other requirements,[2] or must be one that is (i) classified in category I for safety and effectiveness under a tentative final monograph that is the most recently applicable proposal or determination issued under part 330, and (ii) in conformity with the proposed requirements for nonprescription use of such tentative final monograph and any applicable subsequent determination by the Secretary, as well as other requirements.[3] Other applicable requirements in section 505G(a)(1) of the FD&C Act include conditions or requirements under section 505G(b) of the FD&C Act.

Complementary to the requirements for conformity to tentative final or final monographs described in section 505G(a)(1) and (2) of the FD&C Act, Congress provided that, under section 505G(b)(8) of the FD&C Act, a final monograph or tentative final monograph that establishes

[1] Section 505G(a)(2) of the FD&C Act is inapplicable here. It establishes the applicable requirements in terms of conformity with a final monograph, for purposes of section 505G(a)(1)(A)(i) of the FD&C Act, for sunscreen drugs subject to section 505G of the FD&C Act.
[2] Section 505G(a)(1)(A) of the FD&C Act.
[3] Section 505G(a)(1)(B) of the FD&C Act.

conditions of use for a drug described in section 505G(a)(1) or (2) and that represents the most recently promulgated version of the conditions of use, including as modified, in whole or in part, by any proposed or final rule, is deemed to be a final order. The final order may be amended, revoked, or otherwise modified in accordance with the procedures under section 505G of the FD&C Act. Under section 505G(b)(8)(C) of the FD&C Act, the deemed establishment of a final order is construed to include technical amendments necessary to ensure that the order is appropriately harmonized, in terms of terminology or cross-references, with the applicable provisions of the FD&C Act (and regulations) and any other final orders issued under section 505G of the FD&C Act.

In the *Federal Register* of October 6, 1995 (60 FR 52507), FDA issued a final OTC monograph under the procedure in part 330, establishing conditions under which OTC anticaries drug products are generally recognized as safe and effective (GRASE). This final OTC monograph was codified in 21 CFR part 355 and subsequently amended by final rules issued on November 24, 1995 (60 FR 57927), October 7, 1996 (61 FR 52286), March 17, 1999 (64 FR 13296), and May 9, 2003 (68 FR 24879).

Accordingly, this final order for OTC anticaries drug products incorporates the requirements of the final monograph for OTC anticaries drug products issued under part 330, as codified in part 355 as of March 27, 2020, with technical amendments including consolidating professional use provisions into its own part.

III. Final Administrative Order

Over-the-Counter Monograph M021:

Anticaries Drug Products for Over-the-Counter Human Use

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SOURCE: 60 FR 52507, Oct. 6, 1995, unless otherwise noted.

Part A—General Provisions

§ M021.1 Scope

An over-the-counter (OTC) anticaries drug product in a form suitable for topical administration to the teeth is generally recognized as safe and effective and is not misbranded if it meets each condition in this OTC monograph and each general condition established in 21 CFR 330.1.

§ M021.3 Definitions

As used in this OTC monograph:

(a) Abrasive. Solid materials that are added to dentifrices to facilitate mechanical removal of dental plaque, debris, and stain from tooth surfaces.

(b) Anhydrous glycerin. An ingredient that may be prepared by heating glycerin USP at 150° C for 2 hours to drive off the moisture content.

(c) Anticaries drug. A drug that aids in the prevention and prophylactic treatment of dental cavities (decay, caries).

(d) Dental caries. A disease of calcified tissues of teeth characterized by demineralization of the inorganic portion and destruction of the organic matrix.

(e) Dentifrice. An abrasive-containing dosage form (gel, paste, or powder) for delivering an anticaries drug to the teeth.

(f) Fluoride. The inorganic form of the chemical element fluorine in combination with other elements.

(g) Fluoride ion. The negatively charged atom of the chemical element fluorine.

(h) Fluoride supplement. A special treatment rinse dosage form that is intended to be swallowed, and is promoted to health professionals for use in areas where the water supply contains 0 to 0.7 parts per million (ppm) fluoride ion.

(i) Preventive treatment gel. A dosage form for delivering an anticaries drug to the teeth. Preventive treatment gels are formulated in an anhydrous glycerin base with suitable thickening agents included to adjust viscosity. Preventive treatment gels do not contain abrasives.

(j) Treatment rinse. A liquid dosage form for delivering an anticaries drug to the teeth.

(k) Treatment rinse concentrated solution. A fluoride treatment rinse in a concentrated form to be mixed with water before using to result in the appropriate fluoride concentration specified in the OTC monograph.

(l) Treatment rinse effervescent tablets. A fluoride treatment rinse prepared by adding an effervescent tablet (a concentrated solid dosage form) to water before using to result in the appropriate fluoride concentration specified in the OTC monograph.

(m) Treatment rinse powder. A fluoride treatment rinse prepared by adding the powder (a concentrated solid dosage form) to water before using to result in the appropriate fluoride concentration specified in the OTC monograph.

[60 FR 52507, Oct. 6, 1995, as amended at 61 FR 52286, Oct. 7, 1996]

Part B—Active Ingredients

§ M021.10 Anticaries active ingredients

The active ingredient of the product consists of any of the following when used in the concentration and dosage form established for each ingredient:

(a) Sodium fluoride.

(1) Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a gel or paste dosage form. Sodium fluoride 0.188 to 0.254% with an available fluoride ion concentration ≥650 parts ppm.

(2) Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a powdered dosage form. Sodium fluoride 0.188 to 0.254% with an available fluoride ion concentration of ≥850 ppm for products containing the abrasive sodium bicarbonate and a poured-bulk density of 1.0 to 1.2 grams per milliliter.

(3) Treatment rinses.

(i) An aqueous solution of acidulated phosphate fluoride derived from sodium fluoride acidulated with a mixture of sodium phosphate, monobasic, and phosphoric acid to a level of 0.1 molar phosphate ion and a pH of 3.0 to 4.5 and which yields an effective fluoride ion concentration of 0.02%.

(ii) An aqueous solution of acidulated phosphate fluoride derived from sodium fluoride acidulated with a mixture of sodium phosphate, dibasic, and phosphoric acid to a pH of 3.5 and which yields an effective fluoride ion concentration of 0.01%.

(iii) Sodium fluoride 0.02% aqueous solution with a pH of approximately 7.

(iv) Sodium fluoride 0.05% aqueous solution with a pH of approximately 7.

(v) Sodium fluoride concentrate containing adequate directions for mixing with water before using to result in a 0.02% or 0.05% aqueous solution with a pH of approximately 7.

(b) Sodium monofluorophosphate.

(1) Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a gel or paste dosage form. Sodium monofluorophosphate 0.654 to 0.884% with an available fluoride ion concentration (consisting of $PO_3F^{=}$ and F^{-} combined) ≥800 ppm.

(2) Dentifrices containing 1,500 ppm theoretical total fluorine in a gel or paste dosage form. Sodium monofluorophosphate 1.153% with an available fluoride ion concentration (consisting of $PO_3F^{=}$ and F^{-} combined) ≥1,275 ppm.

(c) Stannous fluoride.

(1) Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a gel or paste dosage form.

(i) Stannous fluoride 0.351 to 0.474% with an available fluoride ion concentration ≥700 ppm for products containing abrasives other than calcium pyrophosphate.

(ii) Stannous fluoride 0.351 to 0.474% with an available fluoride ion concentration ≥290 ppm for products containing the abrasive calcium pyrophosphate.

(2) Preventive treatment gel. Stannous fluoride 0.4% in an anhydrous glycerin gel, made from anhydrous glycerin and the addition of suitable thickening agents to adjust viscosity.

(3) Treatment rinse. Stannous fluoride concentrate marketed in a stable form and containing adequate directions for mixing with water immediately before using to result in a 0.1% aqueous solution.

[60 FR 52507, Oct. 6, 1995, as amended at 61 FR 52286, Oct. 7, 1996]

§ M021.20 Packaging conditions

(a) Package size limitation. Due to the toxicity associated with fluoride active ingredients, the following package size limitations are required for anticaries drug products:

(1) Dentifrices. Dentifrice (toothpastes and tooth powders) packages shall not contain more than 276 milligrams (mg) total fluorine per package.

(2) Preventive treatment gels and treatment rinses. Preventive treatment gel and treatment rinse packages shall not contain more than 120 mg total fluorine per package.

(3) Exception. Package size limitations do not apply to anticaries drug products marketed for professional office use only and labeled in accord with § M021.75.

(b) Tight container packaging. To minimize moisture contamination, all fluoride powdered dentifrices shall be packaged in a tight container as defined as a container that protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight reclosure.

Part C—Labeling

§ M021.50 Labeling of anticaries drug products

(a) Statement of identity. The labeling of the product contains the established name of the drug, if any, and identifies the product as: (select one or both of the following: “anticavity” or “fluoride”) (select one of the following as appropriate: “dentifrice,” “toothpaste,” “tooth polish,” “tooth powder;” (optional: “dental”) “preventive treatment gel;” or (optional: “preventive treatment” or “dental”)) (select one of the following: “rinse,” “concentrated solution,” “rinse powder,” or “rinse effervescent tablets”). The word “mouthwash” may be substituted for the word “rinse” in this statement of identity if the product also has a cosmetic use, as defined in section 201(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(i)).

(b) Indication. The labeling of the product states, under the heading “Uses,” the following: “Aids in the prevention of dental (select one of the following: “cavities,” “decay,” “caries (decay),” or “caries (cavities)”). Other truthful and nonmisleading statements, describing only the indication for use that has been established and listed in § M021.50(b), may also be used, as provided in 21 CFR 330.1(c)(2), subject to the provisions of section 502 of the FD&C Act (21 U.S.C. 352) relating to misbranding and the prohibition in section 301(d) of the FD&C Act (21 U.S.C. 331(d)) against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the FD&C Act (21 U.S.C. 355(a)).

(c) Warning. The labeling of the product contains the following warning under the heading "Warning":

(1) For all fluoride dentifrice (gel, paste, and powder) products. "Keep out of reach of children under 6 years of age. [highlighted in bold type] If more than used for brushing is accidentally swallowed, get medical help or contact a Poison Control Center right away." These warnings shall be used in place of the general warning statements required by 21 CFR 330.1(g).

(2) For all fluoride rinse and preventive treatment gel products. "Keep out of reach of children. [highlighted in bold type] If more than used for" (select appropriate word: "brushing" or "rinsing") "is accidentally swallowed, get medical help or contact a Poison Control Center right away." These warnings shall be used in place of the general warning statements required by 21 CFR 330.1(g).

(d) Directions. The labeling of the product contains the following statements under the heading "Directions":

(1) For anticaries dentifrice products

(i) Gel or paste dosage form with a theoretical total fluorine concentration of 850 to 1,150 ppm identified in §§ M021.10(a)(1), (b)(1), and (c)(1). 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 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 years of age: Consult a dentist or doctor.

(ii) Gel or paste dosage form with a theoretical total fluorine concentration of 1,500 ppm identified in § M021.10(b)(2). Adults and children 6 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 12 years of age in good brushing and rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: Do not use unless directed by a dentist or doctor.

(iii) Powdered dosage form with a theoretical total fluorine concentration of 850 to 1,150 ppm identified in § M021.10(a)(2). Adults and children 6 years of age and older: Apply powder to a wet toothbrush; completely cover all bristles. Brush for at least 30 seconds. Reapply powder as before and brush again. Rinse and spit out thoroughly. Brush teeth, preferably after each meal or at least twice a day, or as directed by a dentist or doctor. Instruct children under 12 years of age in good brushing and rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: Do not use unless directed by a dentist or doctor.

(2) For anticaries treatment rinse products

(i) For acidulated phosphate fluoride solution containing 0.02% fluoride ion, sodium fluoride 0.05%, sodium fluoride concentrate, and stannous fluoride concentrate identified in §§ M021.10(a)(3)(i), (a)(3)(iv), (a)(3)(v), and (c)(3). Adults and children 6 years of age and older: Use once a day after brushing your teeth with a toothpaste. Vigorously swish 10 milliliters of rinse between your teeth for 1 minute and then spit out. Do not swallow the rinse. Do not eat or drink for 30 minutes after rinsing. Instruct children under 12 years of age in good rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: Consult a dentist or doctor.

(ii) For acidulated phosphate fluoride solution containing 0.01% fluoride ion and sodium fluoride 0.02% aqueous solution identified in §§ M021.10(a)(3)(ii) and (a)(3)(iii). Adults and children 6 years of age and older: Use twice a day after brushing your teeth with a toothpaste. Vigorously swish 10 milliliters of rinse between your teeth for 1 minute and then spit out. Do not swallow the rinse. Do not eat or drink for 30 minutes after rinsing. Instruct children under 12 years of age in good rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: consult a dentist or doctor.

(3) For stannous fluoride treatment rinse products.

(i) “Use immediately after preparing the rinse.”

(ii) For powder or effervescent tablets used to prepare treatment rinses. “Do not use as a rinse until all the” (select one of the following: “powder” or “tablet”) “has dissolved.”

(4) For anticaries preventive treatment gel products. Adults and children 6 years of age and older: Use once a day after brushing your teeth with a toothpaste. Apply the gel to your teeth and brush thoroughly. Allow the gel to remain on your teeth for 1 minute and then spit out. Do not swallow the gel. Do not eat or drink for 30 minutes after brushing. Instruct children under 12 years of age in the use of this product (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: consult a dentist or doctor.

(5) For all concentrated treatment rinse solutions, powders, and effervescent tablets. The following statement shall appear as the first statement under directions: “Do not use before mixing with water.”

(e) Additional labeling statements for anticaries drug products. The following statements need not appear under warnings, but are required to appear on the label of anticaries drugs products as applicable.

(1) For all preventive treatment gels. “This is a(n)” (select one or both of the following: “anticavity” or “fluoride”) “preventive treatment gel, not a toothpaste. Read directions carefully before using.”

(2) For all stannous fluoride treatment rinse, preventive treatment gel, and dentifrice products. “This product 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.”

(f) Optional additional labeling statements.

(1) For fluoride treatment rinses and preventive treatment gels. The following labeling statement may appear in the required boxed area designated “APPROVED USES”: “The combined daily use of a fluoride preventive treatment” (select one of the following: “rinse” or “gel”) “and a fluoride toothpaste can help reduce the incidence of dental cavities.”

(2) For dentifrice products containing 1,500 ppm theoretical total fluorine. “Adults and children over 6 years of age may wish to use this extra-strength fluoride dentifrice if they reside in a nonfluoridated area or if they have a greater tendency to develop cavities.”

[60 FR 52507, Oct. 6, 1995; 60 FR 57927, Nov. 24, 1995; 61 FR 52287, Oct. 7, 1996; 64 FR 13296, Mar. 17, 1999]

§ M021.55 Principal display panel of all fluoride rinse drug products

In addition to the statement of identity required in § M021.50, the following statement shall be prominently placed on the principal display panel: “IMPORTANT: Read directions for proper use.”

Part D—Testing Procedures

§ M021.70 Testing procedures for fluoride dentifrice drug products

(a) A fluoride dentifrice drug product shall meet the biological test requirements for animal caries reduction and one of the following tests: Enamel solubility reduction or fluoride enamel uptake. The testing procedures for these biological tests are labeled Biological Testing Procedures for Fluoride Dentifrices. These guidelines are available in the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/index.cfm, located under the Supporting Documents tab for Final Administrative Order OTC000034.

(b) The United States Pharmacopeia fluoride dentifrice reference standards along with reference standard stability profiles (total fluoride, available fluoride ion, pH, and specific gravity) required to be used in the biological tests are available to any purchaser upon written request to the United States Pharmacopeia12601 Twinbrook Parkway, Rockville, MD 20852.

(c) Alternative testing procedures may be used. Any proposed modification or alternative testing procedures shall be submitted as a petition in accord with 21 CFR 10.30 or in accord with section 505G(b)(5) of the FD&C Act (21 U.S.C. 355h(b)), as applicable. The submission should contain data to support the modification or data demonstrating that an alternative testing procedure provides results of equivalent accuracy.

[60 FR 52507, Oct. 6, 1995, as amended at 68 FR 24879, May 9, 2003]

Part E—Professional Use

§ M021.75 Professional labeling

(a) The labeling for anticaries fluoride treatment rinses identified in §§ M021.10(a)(3) and (c)(3) that are specially formulated so they may be swallowed (fluoride supplements) and are provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 3 to under 14 years of age: As a supplement in areas where the water supply is nonfluoridated (less than 0.3 parts per million (ppm)), clean the teeth with a toothpaste and rinse with 5 milliliters (mL) of 0.02% or 10 mL of 0.01% fluoride ion rinse daily, then swallow. When the water supply contains 0.3 to 0.7 ppm fluoride ion, reduce the dose to 2.5 mL of 0.02% or 5 mL of 0.01% fluoride ion rinse daily.

(b) The labeling for products marketed to health professionals in package sizes larger than those specified in § M021.20 shall include the statements: “For Professional Office Use Only” and “This product is not intended for home or unsupervised consumer use.”