NATURAL HEALTH PRODUCT

ORAL HEALTH PRODUCTS

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product (NHP) market authorization. It is not intended to be a comprehensive review of the medicinal ingredient.

Note
- Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant’s discretion.
- The solidus (/) indicates that the terms and/or the statements are synonymous. Either term or statement may be selected by the applicant.

Date
December 16, 2014

Table 1  Proper name(s), common name(s), source material(s)

<table>
<thead>
<tr>
<th>Proper name(s)</th>
<th>Common name(s)</th>
<th>Source material(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidulated phosphate fluoride¹ (USP 32)</td>
<td>Acidulated phosphate fluoride (USP 32)</td>
<td>Acidulated phosphate fluoride* (USP 32)</td>
</tr>
<tr>
<td>Nitric acid potassium salt (1:1) (Merck 2012; USP 34; Gottschalck and Bailey 2008)</td>
<td>Potassium nitrate (Merck 2012; USP 34; Gottschalck and Bailey 2008)</td>
<td>Potassium nitrate* (Merck 2012; USP 34; Gottschalck and Bailey 2008)</td>
</tr>
<tr>
<td>Sodium fluoride (Merck 2012; USP 32; Gottschalck and McEwen 2006)</td>
<td>Sodium fluoride (Merck 2012; USP 32; Gottschalck and McEwen 2006)</td>
<td>Sodium fluoride* (Merck 2012; USP 32; Gottschalck and McEwen 2006) CAS No. 7681-49-4⁺</td>
</tr>
<tr>
<td>Phosphorofluoridic acid, disodium salt (USP 32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disodium phosphorofluoridate (USP 32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stannous fluoride (Merck 2012; USP 32;</td>
<td>Stannous fluoride (Merck 2012; USP 32;</td>
<td>Stannous fluoride* (Merck 2012; USP 32;</td>
</tr>
<tr>
<td>Proper name(s)</td>
<td>Common name(s)</td>
<td>Source material(s)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Gottschalck and McEwen 2006;</td>
<td>Gottschalck and McEwen 2006;</td>
<td>Gottschalck and McEwen 2006;</td>
</tr>
<tr>
<td>Tin (II)-fluoride (Merck 2012)</td>
<td>Tin fluoride (Merck 2012)</td>
<td>CAS No. 7783-47-3</td>
</tr>
<tr>
<td>Tin difluoride (Merck 2012)</td>
<td>Tin difluoride (Merck 2012)</td>
<td></td>
</tr>
</tbody>
</table>

*Ingredient must be pharmacopoeial grade (see Specifications).
+The CAS number may be provided as additional information.
1Acidulated phosphate fluoride is derived from sodium fluoride acidulated with a mixture of sodium phosphate dibasic or monobasic and phosphoric acid to a level of 0.1 molar phosphate to yield a pH of 3.0 to 4.5 (FDA 1995).

**Route(s) of administration**

Dental

**Dosage form(s)**

*Products containing Potassium nitrate*

Dentifrice paste (toothpaste), dentifrice gel, treatment rinse, concentrated treatment rinse (solution, effervescent tablet, or powder), mouthwash (rinse)

*All other Products*

Dentifrice paste (toothpaste), dentifrice gel, preventive treatment gel, treatment rinse, concentrated treatment rinse (solution, effervescent tablet, or powder), mouthwash (rinse) (FDA 1995).

**Note**

Refer to Annex 1 for definitions.

**Use(s) or Purpose(s)**

Statement(s) to the effect of

*Products containing Potassium nitrate*

- Helps reduce (painful) sensitivity of the teeth to cold, heat, acids, sweets, or contact (Silverman et al. 1996; Nagata et al. 1994; FDA 1991).
- Builds protection against (painful) sensitivity of the teeth to cold, heat, acids, sweets, or contact (Palé et al. 2013; FDA 1991).
 Effective protection against (painful) sensitivity of the teeth to cold, heat, acids, sweets, or contact (Palé et al. 2013; FDA 1991).


All other products

- Anti-cavity/Anti-caries (IOM 1997; Zimmerman 1992)
- Prevents, fights and/or protects against cavities/caries (Sweetman 2007; FDA 1995; Zimmerman 1992).
- Reduces the incidence of cavities/caries (Sweetman 2007; FDA 1995; Zimmerman 1992).
- Effective fluoride protection (FDA 1995).
- Effective decay preventive fluoride (FDA 1995).
- Helps reverse the tooth decay process at the earliest stage before it can become a cavity (IOM 1997).
- Penetrates tooth enamel to help rebuild weak spots (Sweetman 2007; Zimmerman 1992).
- Protects teeth from acid wear/erosion (Sweetman 2007; IOM 1997; Zimmerman 1992).

Note

- Product labels must contain at least one of the above uses or purposes.
- Claims that are cosmetic in nature such as “whitens teeth” or “refreshes mouth” are acceptable as additional information, provided that these claims are true and verifiable.

Dose(s)

Subpopulation

Dentifrice products that do not contain Potassium nitrate

Adults and children 2 years of age and older (FDA 1995).

Products that do not contain Potassium nitrate in the following dosage forms: Preventive treatment gel; treatment rinse; concentrated treatment rinse, mouthwash (rinse)

Adults and children 6 years of age and older (FDA 1995).

Products containing Potassium nitrate

Adults and children 12 years of age and older (FDA 1991).

Quantity(ies)

Note
- Quantity (%) is required on the Product Licence Application (PLA) and product label.
- For fluoride containing products, Theoretical Total Fluoride and Available Fluoride Ion are both required on the PLA and may be included on the product label as additional optional information.

Table 2  Dose information for dentifrice (gel or (tooth)paste)*

<table>
<thead>
<tr>
<th>Medicinal ingredient</th>
<th>Quantity (% w/w)</th>
<th>Theoretical Total Fluoride (mg/kg)</th>
<th>Available Fluoride Ion (mg/kg¹)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium nitrate</td>
<td>5</td>
<td>N/A</td>
<td>N/A</td>
<td>Minimum twice a day</td>
</tr>
<tr>
<td>Sodium fluoride</td>
<td>0.188 – 0.254</td>
<td>850 – 1150</td>
<td>≥ 650</td>
<td>Minimum twice a day</td>
</tr>
<tr>
<td>Sodium monofluorophosphate</td>
<td>0.654 – 0.884</td>
<td>850 – 1150</td>
<td>≥ 800²</td>
<td>Minimum twice a day</td>
</tr>
<tr>
<td>Stannous fluoride</td>
<td>0.351 – 0.474</td>
<td>850 – 1150</td>
<td>≥ 700³ 290⁴</td>
<td>Minimum twice a day</td>
</tr>
</tbody>
</table>

*Based on FDA1995
¹ mg/kg = ppm
² PO₃F⁻ and F⁻ combined
³ For products containing abrasives other than calcium pyrophosphate
⁴ For products containing the abrasive calcium pyrophosphate

Note: End of Shelf life minimal fluoride Ion values in mg/kg can be included as additional information on the label but are not required on the PLA. These values are intended for determining expiration dating and are not to be used for determining safety and efficacy. See Appendix 2.

Table 3  Dose information for preventive treatment gel, treatment rinse and concentrated treatment rinse (solution, effervescent tablet, or powder), mouthwash (rinse)*

<table>
<thead>
<tr>
<th>Medicinal ingredient</th>
<th>Quantity (% w/w)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium nitrate</td>
<td>3</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Sodium fluoride</td>
<td>0.02 0.05 0.2*</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Concentrated treatment rinse¹</td>
<td>Diluted in water to 0.02 Diluted in water to 0.05 Diluted in water to 0.2*</td>
<td>Once a day Once a week Twice a day</td>
</tr>
</tbody>
</table>

¹ For products containing the abrasive calcium pyrophosphate

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### Medicinal ingredient

<table>
<thead>
<tr>
<th>Medicinal ingredient</th>
<th>Quantity (% w/w)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidulated phosphate fluoride</td>
<td>0.01</td>
<td>Twice a day</td>
</tr>
<tr>
<td>0.02</td>
<td>Once a day</td>
<td></td>
</tr>
<tr>
<td>Stannous fluoride</td>
<td>0.4&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Once a day</td>
</tr>
<tr>
<td>Concentrated treatment rinse&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Diluted in water to 0.1</td>
<td>Once a day</td>
</tr>
</tbody>
</table>


<sup>1</sup> For concentrated treatment rinse products requiring dilution: The labels must contain the quantity of the product before and after dilution as well as the appropriate dilution directions.

<sup>2</sup> In preventive treatment gel form only.

### Permitted combinations

- Potassium nitrate can be combined with any one of the ingredient indicated in Table 2 or Table 3.
- Other combinations must be assessed through the non-compendial stream of the Natural and Non-prescription Health Products Directorate (NNHPD).

### Directions for use

**Statement(s) to the effect of**

**All products**

- Do not swallow (FDA 1995).
- Optional: Should be used as part of an oral health program that includes regular flossing and dental check-ups (CDA 2014).

**Dentifrice products**

Brush teeth thoroughly (for at least 1 minute), preferably after each meal, or as directed by a health care practitioner (FDA 1995).

**Dentifrice products that do not contain Potassium nitrate**

- Children under 6 years of age should use only a pea-sized amount and be supervised to brush properly and to not swallow (CDA 2014).
- Optional: Consult a health care practitioner before using in children under 2 years of age (FDA 1995).

**Preventive treatment gels; treatment rinses; concentrated treatment rinses, mouthwash (rinse) products**

- Use after brushing teeth with toothpaste (Smith 2002; FDA 1995).
- Do not eat, drink or rinse with water for 30 minutes after use (Smith 2002; FDA 1995).
- Instruct children under 12 years of age in the proper use of the product and in good brushing and rinsing habits to minimize swallowing (Smith 2002; FDA 1995).
- Weekly rinses with 0.2% sodium fluoride: Not recommended for use in children under 6 years of age (Sweetman 2007).
- Daily rinses with 0.02% and 0.05% sodium fluoride (optional): Consult a health care practitioner before using in children under 6 years of age (Smith 2002; FDA 1995).
- Products containing potassium nitrate: Not recommended for children under 12 years of age (FDA 1995).

**Preventive treatment gel products**

Apply the gel to teeth and brush thoroughly. Allow the gel to remain on the teeth for 1 minute and then spit out (Smith 2002; FDA 1995).

**Treatment rinses; concentrated treatment rinses (after proper dilution), mouthwash (rinse) products**

Swish approximately 10 ml of rinse vigorously around and between the teeth for 1 minute and then spit out (Smith 2002; FDA 1995).

**Concentrated treatment rinse products in a solution; effervescent tablet; powder dosage form**

- Do not use before mixing with water and/or until all the tablet/powder has dissolved completely (FDA 1995).
- Use immediately after preparing the rinse (FDA 1995).

**Duration of use**

No statement required.

**Risk information** Statement(s) to the effect of

**Caution(s) and warning(s)**

**Dentifrice products that do not contain Potassium nitrate**

- Keep out of reach of children under 6 years of age.
- If a quantity greater than the dose used for brushing is accidentally swallowed, get medical help or contact a Poison Control Centre right away (FDA 1995).

**Products containing Potassium nitrate**

- If symptoms persist or worsen, consult a dentist (FDA 1991).
- Keep out of reach of children.

**Preventive treatment gels; treatment rinses; concentrated treatment rinses, mouthwash (rinse) products**

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Keep out of reach of children.
If a quantity greater than the dose used for brushing and/or rinsing is accidentally swallowed, get medical help or contact a Poison Control Centre right away (FDA 1995).

**Preventive treatment gels containing stannous fluoride**

This product may produce surface staining of the teeth. Adequate brushing may prevent these stains which are harmless and temporary and may be removed by a dental care practitioner (FDA 1995).

**Products containing more than the equivalent of 120 mg of fluoride ion, except those in toothpaste form (includes dentifrice paste and dentifrice gel)**

Keep out of reach of children. This product contains enough fluoride to seriously harm a child. (Note: These cautionary statements shall be preceded by a prominently displayed symbol that is octagonal in shape, conspicuous in colour and on a background of a contrasting colour. If the product is recommended solely for children, all package sizes must be packaged in a child-resistant package (CRP). If the product is not recommended solely for children, at least one of the sizes of packages available for sale must be packaged in CRP and all other package sizes must carry a statement that the NHP is available in a CRP, as per Section 97 of the Natural Health Product Regulations, citing Sections C.01.029, C.01.031 and C.01.031.2 (1) of the Food and Drug Regulations (JC 2014)).

**Contraindication(s)**

No statement required.

**Known adverse reaction(s)**

No statement required.

**Non-medicinal ingredients**

- The International Nomenclature for Cosmetic Ingredients (INCI) is acceptable.
- Non medicinal ingredients must be chosen from the current NNHPD Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in the database.
- Other ingredients currently accepted as cosmetic ingredients will also be considered.

**Specifications**

- The finished product specifications must be established in accordance with the requirements described in the NNHPD Quality of Natural Health Products Guide.
- The medicinal ingredient must comply with the requirements outlined in the Natural Health
Products Ingredients Database (NHPID).

- The medicinal ingredient must either:
  
  i. Comply with the specifications outlined in the monographs published in the British (BP), European (Ph. Eur.) or United States (USP) pharmacopoeias (Table 4 below); or,
  
  ii. Be cited in an approved NHP Master File, authorized by a letter of access issued to the applicant by the NHP Master File's registered owner.

- This monograph describes those requirements that are specific to this class of natural health products (NHPs). Any change to the manufacturing process that impacts the safety and efficacy of the ingredients, such as the use of novel technology (e.g. nanotechnology), requires supporting data and will be reviewed outside the monograph.

- Diethylene glycol (DEG) is not acceptable as a non-medicinal ingredient. Product licence applicants must have a copy of a Certificate of Analysis or any other equivalent document confirming the absence of DEG in the finished product on file. This information is not to be submitted with the compendial Product Licence Application, although it may be requested at the NNHPD’s discretion.

- Products containing glycerin as a non-medicinal ingredient must meet the specifications as outlined in the United States Pharmacopoeia.

Table 4  Monographs published in the British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.) and the U.S. Pharmacopoeia (USP)

<table>
<thead>
<tr>
<th>Pharmacopeia</th>
<th>Monograph</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>Sodium Fluoride</td>
</tr>
<tr>
<td>Ph. Eur.</td>
<td>Potassium nitrate</td>
</tr>
<tr>
<td>USP</td>
<td>Sodium Fluoride</td>
</tr>
<tr>
<td></td>
<td>Sodium Fluoride Oral Solution</td>
</tr>
<tr>
<td></td>
<td>Sodium Fluoride Tablets</td>
</tr>
<tr>
<td></td>
<td>Sodium Fluoride and Phosphoric Acid Gel</td>
</tr>
<tr>
<td></td>
<td>Sodium Monofluorophosphate</td>
</tr>
<tr>
<td></td>
<td>Stannous Fluoride</td>
</tr>
<tr>
<td></td>
<td>Stannous Fluoride Gel</td>
</tr>
<tr>
<td></td>
<td>Potassium nitrate</td>
</tr>
</tbody>
</table>
References cited


References reviewed


Appendix 1

Definitions

Dentifrice
An abrasive-containing dosage form (gel or paste) for delivering a medicinal agent to the teeth (FDA 1995), e.g. toothpaste.

Mouthwash
An aqueous solution of one or more active ingredients intended, usually after dilution with warm water, for use in contact with the mucous membranes of the oral cavity, including gargling. Most often used for its deodorant, refreshing, or antiseptic effect.

Preventive treatment gel
A dosage form for delivering a medicinal agent to the teeth. Preventive treatment gels are formulated in an anhydrous glycerine base with suitable thickening agents included to adjust viscosity. Preventive treatment gels do not contain abrasives (FDA 1995).

Treatment rinse
A liquid dosage form for delivering a medicinal agent to the teeth (FDA 1995).

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 monograph (FDA 1995).

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 monograph (FDA 1995).

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 monograph (FDA 1995).
### Appendix 2

<table>
<thead>
<tr>
<th>Medicinal ingredient</th>
<th>End-of-Shelf Life Minimal Fluoride Ion (mg/kg(^1))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium nitrate</td>
<td>N/A</td>
</tr>
<tr>
<td>Sodium fluoride</td>
<td>≥ 403</td>
</tr>
<tr>
<td>Sodium monofluorophosphate</td>
<td>≥ 600</td>
</tr>
<tr>
<td>Stannous fluoride</td>
<td>≥ 650(^2)</td>
</tr>
<tr>
<td></td>
<td>≥ 108(^3)</td>
</tr>
</tbody>
</table>

\(^1\) mg/kg = ppm  
\(^2\) For products containing abrasives other than calcium pyrophosphate  
\(^3\) For products containing the abrasive calcium pyrophosphate