Public Assessment Report

UKPAR

Fluoride 2800 ppm Toothpaste
Fluoride 5000 ppm Toothpaste

(Sodium fluoride)

UK Licence No: PL 20117/0239-0240

Morningside Healthcare Limited
LAY SUMMARY

Fluoride 2800 ppm and 5000 ppm Toothpaste
(Sodium fluoride, toothpaste, 2800 ppm and 5000 ppm)

This is a summary of the Public Assessment Report (PAR) for Fluoride 2800 ppm (parts per million) Toothpaste (PL 20117/0239) and Fluoride 5000 ppm (parts per million) Toothpaste (PL 20117/0240). It explains how Fluoride 2800 ppm and 5000 ppm Toothpaste were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Fluoride 2800 ppm and 5000 ppm Toothpaste.

For practical information about using Fluoride 2800 ppm and 5000 ppm Toothpaste, patients should read the package leaflet or contact their doctor or pharmacist.

What are Fluoride 2800 ppm and 5000 ppm Toothpaste and what are they used for?
Fluoride 2800 ppm and 5000 ppm Toothpaste are medicines with ‘well established use’. This means that the medicinal use of the active substance fluoride (as sodium fluoride) is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Fluoride 2800 ppm Toothpaste:
Fluoride 2800 ppm Toothpaste is used for the prevention and treatment of tooth decay (dental caries) of the tooth crown and root in children and adolescents aged 10 years and older.

Fluoride 5000 ppm Toothpaste:
Fluoride 5000 ppm Toothpaste is used to help prevent tooth decay (dental caries) in adolescents aged 16 years and older, and adults, particularly amongst patients at risk from multiple caries.

How do Fluoride 2800 ppm and 5000 ppm Toothpaste work?
Fluoride 2800 ppm and 5000 ppm Toothpaste contain the active ingredient fluoride (as sodium fluoride) which belongs to a group of medicines called caries preventing agents. When Fluoride 2800 ppm and 5000 ppm Toothpaste is applied to the teeth, after tooth eruption, it reduces tooth decay (dental caries) by stopping demineralisation and promoting remineralisation of the tooth surface. It is effective on both enamel and exposed dentine (the 2 outer layers that make up part of the tooth).

How is Fluoride 2800 ppm and 5000 ppm Toothpaste used?
The pharmaceutical form of Fluoride 2800 ppm and 5000 ppm Toothpaste is a toothpaste and the route of administration is for application to the teeth (topical).

Fluoride 2800 ppm Toothpaste is only for use by persons aged 10 years and older.

Fluoride 5000 ppm Toothpaste is only for use by persons aged 16 years and older.

The patient must always use this medicine exactly as their doctor, dentist or pharmacist has told them to. The patient must check with their doctor, dentist or pharmacist if they are not sure.

How to use Fluoride 2800 ppm Toothpaste (persons aged 10 years and older):
To be used daily instead of the normal toothpaste.
The patient should brush carefully and thoroughly, for one minute, morning and evening:
  • The patient should apply a 1 cm ribbon of toothpaste onto the toothbrush for each brushing
  • The patient should brush their teeth vertically, from the gum to the tip of the teeth
• Careful brushing takes approximately one minute
• The patient should spit out after use
• For best results the patient should not drink or rinse for 30 minutes

Not to be swallowed.

How to use Fluoride 5000 ppm Toothpaste (persons aged 16 years and older):
The patient should use the toothpaste 3 times a day for brushing their teeth:
• The patient should apply a 2 cm ribbon of toothpaste onto their toothbrush for each brushing (2
  cm provides between 3 mg and 5 mg of fluoride).
• The patient should brush their teeth after each meal
• The patient should brush their teeth vertically, from the gum to the tip of the tooth.
• The patient should spit out excess foam and must not swallow.
• Careful brushing of the teeth should take about 3 minutes.

Not to be swallowed.

Please read section 3 of the package leaflets for detailed information on dosing recommendations, the
route of administration and the duration of treatment.

Fluoride 2800 ppm and 5000 ppm Toothpaste can only be obtained with a prescription.

What benefits of Fluoride 2800 ppm and 5000 ppm Toothpaste have been shown in studies?
As fluoride is a well-known substance, and its use in the treatment of tooth decay (dental caries) of
the tooth crown and root in children and adolescents aged 10 years and older (Fluoride 2800 ppm
Toothpaste) and also to help prevent tooth decay (dental caries) in adolescents aged 16 years and older,
and adults, particularly amongst patients at risk from multiple caries (Fluoride 5000 ppm Toothpaste) is
well established, the applicant presented data from the scientific literature. The literature provided
confirmed the efficacy and safety of the use of fluoride in the treatment and prevention of tooth decay.

What are the possible side effects of Fluoride 2800 ppm and 5000 ppm Toothpaste?
For the full list of all side effects reported with Fluoride 2800 ppm and 5000 ppm Toothpaste, see
section 4 of the package leaflets or the Summaries of Product Characteristics (SmPCs) available on the
MHRA website.

Why was Fluoride 2800 ppm and 5000 ppm Toothpaste approved?
The MHRA decided that Fluoride 2800 ppm and 5000 ppm Toothpaste’s benefits are greater than their
risks and recommended that they be approved for use.

What measures are being taken to ensure the safe and effective use of Fluoride 2800 ppm and 5000
ppm Toothpaste?
A Risk Management Plan has been developed to ensure that Fluoride 2800 ppm and 5000 ppm
Toothpaste are used as safely as possible. Based on this plan, safety information has been included in the
Summaries of Product Characteristics and the package leaflets for Fluoride 2800 ppm and 5000 ppm
Toothpaste, including the appropriate precautions to be followed by healthcare professionals and
patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by
patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Fluoride 2800 ppm and 5000 ppm Toothpaste
Marketing Authorisations for Fluoride 2800 ppm and 5000 ppm Toothpaste were granted on 10 December 2014.

The full PAR for Fluoride 2800 ppm and 5000 ppm Toothpaste follows this summary.

For more information about treatment with Fluoride 2800 ppm and 5000 ppm Toothpaste, read the package leaflets, or contact your doctor, dentist or pharmacist.

This summary was last updated in May 2015.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>I</th>
<th>Introduction</th>
<th>Page 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 6</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 10</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 10</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 12</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and recommendation</td>
<td>Page 12</td>
</tr>
</tbody>
</table>
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Limited Marketing Authorisations for the medicinal products Fluoride 2800 ppm Toothpaste (PL 20117/0239) and Fluoride 5000 ppm Toothpaste (PL 20017/0240) on 10 December 2014. The products are prescription-only medicines (POM) with the following indications:

Fluoride 2800 ppm Toothpaste:
- For the prevention and treatment of dental caries (coronal and root) in adolescents and children aged 10 years or more.

Fluoride 5000 ppm Toothpaste:
- For the prevention of dental caries in adolescents and adults, particularly amongst patients at risk from multiple caries (coronal and/or root caries).

These applications were submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be applications for products containing an active substance of well-established use.

Fluoride is important in fighting tooth decay as it makes the tooth surface harder and thus, helps to prevent cavities. The effect of fluoride on caries incidence, prevalence and progression is well documented. Dental protection is primarily a topical action on the tooth surface. Fluoride exerts its cariostatic effects through the liquid phase surrounding the enamel. Its mechanism of action is based on three principles:

1. inhibiting demineralisation
2. enhancing remineralisation
3. inhibiting bacterial metabolism.

Bibliographic data on fluoride have been submitted to support these applications. No new non-clinical or clinical studies were conducted for these applications, which is acceptable given that these are bibliographic applications for products containing an active ingredient of well-established use.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products.
II QUALITY ASPECTS

II.1 Introduction
Each 1 gram of toothpaste contains 2.8 mg fluoride (as sodium fluoride) corresponding to 2800 ppm fluoride, sodium fluoride 0.619 % w/w or 5 mg fluoride (as sodium fluoride), corresponding to 5000 ppm fluoride, sodium fluoride 1.1 % w/w. Other ingredients consist of the following pharmaceutical excipients:

Fluoride 2800 ppm Toothpaste:
Sorbitol solution [non – crystallising] (E420), glycerol, (E422), dental type silica [precipitated] (E551), macrogol 600 (E1521), sodium laurilsulphate, carmellose sodium (E466), sodium saccharin (E954) titanium dioxide (E171), mint flavour 947093 Optamint Spearmint (containing menthol, propylene glycol, spearmint oil, carvone, anethol, ethyl maltol and vanillin) and purified water.

Fluoride 5000 ppm Toothpaste:
Sorbitol solution [non – crystallising] (E420), dental type silica [precipitated] (E551), macrogol 600, (E1521), tetrapotassium pyrophosphate (E340), xanthan gum (E415), sodium benzoate (E211), sodium laurilsulphate, spearmint flavouring Optamint 948800 (containing menthol, propylene glycol, carvone, spearmint oil, peppermint oil, anethol, and vanillin), saccharin sodium (E954), Brilliant Blue FCF (E133) and purified water.

Both strengths (2800 ppm and 5000 ppm) of the finished product are packed into polyethylene/copolymer/aluminium/copolymer/polyethylene laminated tubes with polypropylene flip top closures in pack sizes of:
- 75 millilitres (ml) for Fluoride 2800 ppm Toothpaste
- 51 g for Fluoride 5000 ppm Toothpaste.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance

INN Sodium fluoride.
Chemical name: Sodium fluoride.
Molecular formula: NaF
Molecular Mass: 41.99 g/mol.
Appearance: A white, solid, crystalline powder.
Solubility: On solution in water, sodium fluoride ionises into Na⁺ and F⁻ ions. Sodium fluoride is insoluble in alcohol.

Sodium fluoride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, sodium fluoride, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, toothpaste containing 2800 ppm or 5000 ppm fluoride (as sodium fluoride) per each 1 gram of toothpaste

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of:

- 2800 ppm strength:
  - the mint flavour 947093 Optamint Spearmint

- 5000 ppm strength:
  - the mint flavour Optamint 948800, tetrapotassium pyrophosphate and the colouring Brilliant Blue FCF

which are controlled to suitable in-house specifications. In addition, all colourings are stated to comply with EU approved specifications for colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient. All primary packaging complies with the current European regulations (Regulation (EU) No. 10/2011).

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot-scale batch size and shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform process validation on future commercial-scale batches.

Finished Product Specifications
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months for the unopened tube which reduces to 6 months once the tube has been opened with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

II.5 Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text for Fluoride 2800 ppm and 5000 ppm Toothpaste:
PAR Fluoride 2800 ppm and 5000 ppm Toothpaste

**Fluoride 5000ppm Toothpaste**

**Toothpaste**

**51g**

MORNINGSIDE HEALTHCARE

**Ingredients:**
- Propylene glycol (E429), water (E127), sodium lauryl macrogol ether (E452), xanthan gum (E415), sodium bicarbonate (E241), octoxynol 9 (E454), sodium saccharin (E960), sodium fluoride (E871)
- For dental use only. Do not swallow.
- Keep out of the sight and reach of children.
- Read the package leaflet before use. Do not use in adolescents and children under 16 years of age.
- This product requires no special storage conditions.

**Packaging Information:**
- PL 20117/0239-0240
- Product code: 2011702390240
- Manufacturer: Morningside Healthcare Ltd., 75 Humber Road, Leicester LE1 4HA, UK

**Batch Details:**
- Batch details printed here.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of sodium fluoride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
The introduction of the generic products, Fluoride 2800 ppm and 5000 ppm Toothpaste, onto the market is unlikely to result in an increase in the combined sales of sodium fluoride-containing products, which in turn is unlikely to lead to an increased exposure of the environment to sodium fluoride. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that these are bibliographic applications for a product containing an active ingredient of well-established use.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
No new clinical pharmacology data, efficacy data or safety data have been submitted and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of sodium fluoride.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
No new pharmacokinetic data were submitted and none were required for an application of this type.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type. The clinical efficacy of sodium fluoride is well-established. Efficacy is adequately reviewed in the clinical overview.
IV.5 Clinical safety

No new safety data were submitted and none were required for these bibliographic applications. Safety is adequately reviewed in the clinical overview. The safety profile of sodium fluoride is well-known.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance system

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Fluoride 2800 ppm and 5000 ppm Toothpaste.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns as approved in the RMP:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
</tr>
<tr>
<td>• Allergic reactions</td>
</tr>
<tr>
<td>• Use in children aged less than 10 years (2800 ppm Fluoride Toothpaste)</td>
</tr>
<tr>
<td>• Use in children and adolescents aged less than 16 years (5000 ppm Fluoride Toothpaste)</td>
</tr>
<tr>
<td>• Fluorosis</td>
</tr>
<tr>
<td>• Use in individuals with fructose intolerance</td>
</tr>
<tr>
<td>Important potential risks</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Important missing information</td>
</tr>
<tr>
<td>Use during pregnancy and breastfeeding and effects on fertility (5000 ppm Fluoride Toothpaste)</td>
</tr>
</tbody>
</table>

Summary table of risk minimisation measures as approved in the RMP:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important Identified Risks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>The risks of allergic reactions associated with the use of the product are described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in children aged less than 10 years (2800 ppm Fluoride Toothpaste)</td>
<td>The risks associated with the use of Fluorodent 2800 ppm Fluoride Toothpaste in children aged less than 10 years are described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in children and adolescents aged less than 16 years (5000 ppm Fluoride Toothpaste)</td>
<td>The risks associated with the use of Fluorodent 5000 ppm Fluoride Toothpaste children and adolescents aged less than 16 years are described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Fluorosis</td>
<td>The risks of fluorosis associated with the use of the product are described in the SmPC, and appropriate advice is provided to the prescriber to minimise</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Use in individuals with fructose intolerance</td>
<td>The risks associated with the use of the product in users with fructose intolerance are described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
</tbody>
</table>

**Important Potential Risks**

None

**Important Missing Information**

Use during pregnancy and breastfeeding and effects on fertility (5000 ppm Fluoride Toothpaste)

The SmPC states that there is no adequate data for use of Fluorodent 5000 ppm Fluoride Toothpaste in pregnant or breastfeeding women or for effects on fertility.

Not applicable

### IV.7 Discussion on the clinical aspects

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

The bibliographic data submitted for these applications does support the claim of well-established use for the sought indications of:

**Fluoride 2800 ppm Toothpaste:**

- ‘For the prevention and treatment of dental caries (coronal and root) in adolescents and children aged 10 years or more.’

**Fluoride 5000 ppm Toothpaste:**

- ‘For the prevention of dental caries in adolescents and adults, particularly amongst patients at risk from multiple caries (coronal and/or root caries).’

The grant of marketing authorisations is recommended for these applications.

### V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

### VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with sodium fluoride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.