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SENSODYNE TOTAL CARE F TOOTHPASTE

PL 00036/0103

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Stafford Miller Limited (trading as GlaxoSmithKline Consumer Healthcare) a Marketing Authorisation (licence) for the medicinal product Sensodyne Total Care F Toothpaste (Product Licence number: 00036/0103). This product is available without prescription and can be bought from pharmacies and other outlets.

If tooth enamel is damaged or worn away the sensitive dentine underneath is exposed. This can lead to pain when teeth come into contact with heat, cold, sweetness, acidity or brushing. Sensodyne Total Care F Toothpaste contains potassium nitrate, which calms the nerve endings inside the dentine, relieving the pain of sensitive teeth. This toothpaste also contains sodium fluoride, which helps prevent tooth decay.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Sensodyne Total Care F Toothpaste outweigh the risks, hence a Marketing Authorisation has been granted.
SENSODYNE TOTAL CARE F TOOTHPASTE

PL 00036/0103

SCIENTIFIC DISCUSSION

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INTRODUCTION

This Marketing Authorisation application is submitted under Article 8.3(i) of Directive 2001/83/EC (as amended), for a known active substance. Sensodyne Total Care F Toothpaste is considered to be a line extension of Sensodyne F Original Low Fluoride (PL 00036/0039), which initially received a UK marketing authorisation on 5 June 1986 under the name Sensodyne F Dentifrice Paste.

Dentinal hypersensitivity can develop when dentine is exposed to the environment of the oral cavity. The potassium ions in potassium nitrate are known to reduce dental hypersensitivity by causing depolarisation of the pulpal sensory nerves, thereby interrupting transmission of the pain stimuli. Sodium fluoride has been widely available as an anti-caries agent in the UK and other European countries since the late 1960’s, being sold alone and in combination with other active ingredients in many products.

Sensodyne Total Care F Toothpaste is a mint flavoured toothpaste containing 5% w/w potassium nitrate and 0.306% w/w sodium fluoride. This application is for a General Sales List (GSL) product.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

**Sodium Fluoride**

Sodium fluoride is a well known, established active ingredient used extensively in toothpastes.

Description: White powder or colourless crystals.

Molecular formula: NaF

Relative molecular mass: 41.99

Sodium fluoride has a European Pharmacopoeia monograph. The proposed specifications are in compliance with the pharmacopoeia monograph.

The analytical methods used are those described in the European Pharmacopoeia. Consequently, no validation has been performed.

Certificates of analysis have been supplied for batches from the active substance manufacturer. All batches are within the specification and show a reasonable degree of conformity.

The active substance manufacturer uses a European Pharmacopoeia reference standard.

Relevant certification has been provided verifying the compliance of the packaging used with the EU requirements for food grade contact materials.

Data from stability studies of sodium fluoride stored in ICH storage conditions support the proposed retest period and storage conditions.

**Potassium nitrate**

Potassium nitrate is a well known, established active ingredient used extensively in toothpastes.

Description: White crystalline powder, white granules or colourless crystals

Molecular formula: KNO₃

Relative molecular mass: 101.10

Potassium nitrate has a European Pharmacopoeia monograph. The proposed specifications are in compliance with the pharmacopoeia monograph.
The analytical methods used are those described in the European Pharmacopoeia. Consequently, no validation has been performed.

Certificates of analysis have been supplied for batches from the active substance manufacturer. All batches are within the specification and show a reasonable degree of conformity.

The active substance manufacturer uses a European Pharmacopoeia reference standard.

Relevant certification has been provided verifying the compliance of the packaging used with the EU requirements for food grade contact materials.

Data from stability studies of potassium nitrate stored in ICH storage conditions support the proposed retest period and storage conditions.

**DRUG PRODUCT**

**Composition**

Other ingredients of the toothpaste consist of pharmaceutical excipients, namely sorbitol liquid (non crystallising), purified water, glycerol, silica (dental type - hydrated), silica (dental type - amorphous), sodium laurilsulfate, xanthan gum, flavour blend 826473, titanium dioxide, macrogol (polyethylene glycol 300), saccharin sodium and cocamidopropyl betaine. The excipients are all commonly used in the manufacture of toothpastes and widely used in the pharmaceutical industry in the production of semi-solid dosage forms.

All of the excipients comply with their respective European Pharmacopoeial monograph, with the exception of cocamidopropyl betaine and flavour blend 826473, which do not have pharmacopoeia monographs. Appropriate in-house tests are used to ensure the quality of cocamidopropyl betaine and flavour blend 826473 (in the absence of a Ph Eur monograph, this is acceptable). Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used in the formulation are of human or animal origin. Relevant documentation have been provided regarding the BSE/TSE status of the materials used.

There are no overages within the formulation.

**Manufacture**

Flow diagrams detailing the manufacturing process have been provided. Written summaries of the process are also included.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out and the results are satisfactory.
Control of finished product
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container closure system
The toothpaste is filled into either a polyethylene plastic barrier laminate tube with a full diameter polypropylene cap (with or without an aluminium or metallised PET tamper evident nozzle seal) or a polypropylene, pump actuated, tamper evident dispenser.

Certification verifying compliance to the EU directives on contact materials has been provided from the suppliers of all the packaging components. The specifications have also been provided from the packaging material manufacturers.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set with the storage precaution ‘Store below 30°C’; this is acceptable.

Conclusions
A Marketing Authorisation can be granted for this product.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for applications of this type.
INTRODUCTION

Indications
This product is indicated for the relief of dental hypersensitivity and as an aid to the prevention of dental caries.

Dose and Dose Regimen
The recommended dosing regimen is use two to four times a day, in place of ordinary toothpaste.

CLINICAL PHARMACOLOGY

Pharmacokinetics
As stated in the CPMP notes for guidance on the non-clinical documentation of medicinal products with well established use (CPMP/SWP/799/95), pharmacological investigations, including pharmacokinetics, are normally not necessary. The Applicant, in keeping with this guidance and the extensive history of safety of potassium nitrate in dentrifice preparations, has not presented any additional pharmacokinetic data.

Pharmacodynamics
No specific clinical pharmacology studies have been conducted on this product.

Bioequivalence
No bioavailability or bioequivalence studies have been conducted on this product.

CLINICAL EFFICACY

No specific clinical studies to investigate the efficacy of the product as an anti-caries product have been conducted, however, there is extensive literature demonstrating that the use of fluoridated toothpastes can lead to significant decreases in the incidence of dental caries and clinical studies have been performed on formulations which are similar to the proposed product.

No specific clinical studies to investigate the desensitising efficacy of the product have been conducted, however, there is extensive clinical evidence (including double-blind, placebo-controlled studies of fluoridated, potassium nitrate-containing toothpastes) that potassium-containing toothpastes can lead to significant decreases in dental hypersensitivity in response to various stimuli.

CLINICAL SAFETY

Formulations similar to the proposed product containing the same levels of sodium fluoride and potassium nitrate are used worldwide by many millions of people each year.
Based on the available preclinical data and the extensive in-use history of potassium nitrate in toothpaste products, it can be clearly concluded that Sensodyne Total Care F containing 5% potassium nitrate is safe for its intended use and is unlikely to cause significant undesirable effects when used as recommended.

The relatively low incidence of reporting of adverse events, when considered together with patient exposure, confirm that potassium nitrate-containing toothpastes do not cause significant undesirable effects when used within the dosage recommendations.

**RISK BENEFIT**
The Applicant has demonstrated that the active ingredients in the proposed product have a well established use with an acceptable level of safety and with a recognised efficacy.

**CONCLUSION**
This product can be granted a Marketing Authorisation.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of the product are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY AND SAFETY

The efficacy of potassium nitrate and sodium fluoride toothpastes has been well documented in the past. No new or unexpected safety concerns arise from this application.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit ratio is considered to be positive.
**SENSODYNE TOTAL CARE F TOOTHPASTE**

**PL 00036/0103**

**STEPS TAKEN FOR ASSESSMENT**

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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 8 February 2005</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 10 February 2005</td>
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<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 18 August 2005</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information the quality dossier on 7 December 2005</td>
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<td>5</td>
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<td>6</td>
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<td>7</td>
<td>Following assessment of the response the MHRA requested further information relating to the clinical dossier on 6 June 2006</td>
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<tr>
<td>8</td>
<td>The applicant responded to the MHRA’s request, providing further information on the quality dossier on 27 June 2006</td>
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<tr>
<td>9</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 19 October 2006</td>
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<tr>
<td>10</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 1 November 2006</td>
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<td>11</td>
<td>Following assessment of the response the MHRA requested further information relating to the clinical dossier on 16 November 2006</td>
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<tr>
<td>12</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 7 March 2007 and the quality dossier on 23 March 2007</td>
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<tr>
<td>13</td>
<td>Following assessment of the response the MHRA requested further information relating to the clinical dossier on 8 March 2007</td>
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<td>14</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 16 April 2007</td>
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<td>15</td>
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<td>2007</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 8 June 2007</td>
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<td>16</td>
<td>The application was determined on 15 August 2007</td>
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<td>17</td>
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</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Sensodyne Total Care F Toothpaste

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Potassium Nitrate 5.0% w/w
Sodium Fluoride 0.306% w/w
For full list of excipients see 6.1

3 PHARMACEUTICAL FORM
Toothpaste.
White paste.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Relief from the pain of dentinal sensitivity, an aid for the prevention of dental caries.

4.2 Posology and method of administration
For Dental Use.
For oromucosal use only.
Use 2-4 times a day, in place of ordinary toothpaste.

4.3 Contraindications
Sensitivity to any of the active ingredients or excipients.

4.4 Special warnings and precautions for use
Sensitive teeth may indicate an underlying problem which needs prompt care by a dentist. See your dentist as soon as possible for advice.
For children under 6, use a pea-sized amount and supervise brushing to minimise swallowing.
If using fluoride supplements consult your dentist.

4.5 Interaction with other medicinal products and other forms of interaction
None known.

4.6 Pregnancy and lactation
No adverse effects known.

4.7 Effects on ability to drive and use machines
None known.

4.8 Undesirable effects
Very rarely, isolated cases of hypersensitivity type reactions such as angioedema, oral and facial swelling have been reported in patients using potassium nitrate containing
toothpastes, particularly in patients who are predisposed to hypersensitivity type reactions.

4.9 Overdose
No symptoms of overdose are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC Code Sodium Fluoride: A01AA01
ATC Code Potassium Nitrate: Not assigned.
The antibacterial formulation contains potassium ions which are thought to reduce hypersensitivity by interfering with pulpal nerve conduction.
It also contains sodium fluoride which is an established anticaries agent.

5.2 Pharmacokinetic properties
The product is applied topically and so the pharmacokinetics of the active ingredients are not relevant to its efficacy.

5.3 Preclinical safety data
The active ingredients in the product are commonly used and well established. Their safety is supported by numerous published studies. Many years of clinical experience with the use of these substances in man supports the opinion that they have a favourable safety profile.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sorbitol
Glycerol
Silica, Dental Type
Purified Water
Sodium Laurilsulfate
Titanium Dioxide (E 171)
Saccharin Sodium
Mint Flavour 826473
Cocamidopropyl Betaine
Xanthan Gum
Macrogol

6.2 Incompatibilities
None known.

6.3 Shelf life
24 months
Shelf-life after opening: 6 months
6.4 **Special precautions for storage**
Store below 30°C.

6.5 **Nature and contents of container**
The product will be packaged in the following containers and pack sizes:

<table>
<thead>
<tr>
<th>Container</th>
<th>Pack sizes (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decorated Polyethylene plastic barrier laminate tubes with a full diameter polypropylene cap with or without an aluminium or metallised PET tamper evident nozzle seal</td>
<td>20, 45, 50, 75, 100</td>
</tr>
<tr>
<td>Polypropylene decorated, pump actuated, tamper evident dispenser</td>
<td>100</td>
</tr>
</tbody>
</table>

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
None.

7 **MARKETING AUTHORISATION HOLDER**
Stafford Miller Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

Trading as: GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, U.K.

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00036/0103

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
15/08/2007

10 **DATE OF REVISION OF THE TEXT**
15/08/2007
20 ml tube:

NEW IMPROVED FLAVOUR
clinically proven relief from the pain of sensitive teeth

LABELLING

Print Free  Pharma Code  Partially Visible

Profile Keys:
**SENSODYNE TOTAL CARE TOOTHPASTE**

**NEW IMPROVED FLAVOUR**

Clinically proven relief from the pain of sensitive teeth

**45 ml tube**

- **Fluoride toothpaste**

- **Flavours**
  - Fresh Mint
  - Spearmint

- **Active ingredient**
  - Fluoride

- **Salts**
  - Sodium bicarbonate
  - Magnesium hydroxide

- **Preservatives**
  - Hydroxypropyl methylcellulose
  - Cetyl alcohol

- **Water**

- **Flavouring agents**
  - Mint extract

- **Other ingredients**
  - Sorbitol

- **Mineral water**

- **Uses**
  - Cleansing
  - Freshening

- **For children under 6, use a pea-sized amount and supervise brushing to minimise swallowing.**

- **Sensitivities**
  - Sensitivities may indicate an underlying problem which needs prompt care by a dentist. See your dentist as soon as possible for advice.

- **Do not use if you are sensitive to any of the ingredients.**

- **Very rarely you might have an allergic reaction, such as swelling of the mouth or face. This is more likely if you have had allergies in the past.**

- **Consult your doctor, dentist or pharmacist if you notice any unwanted effects after using this product.**

- **KEEP OUT OF THE REACH AND SIGHT OF CHILDREN**

- **Do not use after the date shown on end of tube.**
  
  - Use within 6 months of opening.
  
  - Store below 30°C.
  
  - Do not use if gel seal on nozzle is broken.

- **Remove foil before use.**

- **MA Holder: GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, UK. SENSODYNE is a registered trade mark of the GlaxoSmithKline group of companies. Made in U.K.**
100 ml pump:
100 ml carton: