SENSODYNE PRONAMEL TOOTHPASTE
SENSODYNE ENAMEL-PRO TOOTHPASTE

PL 00036/0105
PL 00036/0302

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SENSODYNE ENAMEL-PRO TOOTHPASTE

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Stafford Miller Limited (trading as GlaxoSmithKline Consumer Healthcare) Marketing Authorisations (licences) for the medicinal products Sensodyne Pronamel Toothpaste and Sensodyne Enamel-Pro Toothpaste (Product Licence numbers: 00036/0105 and 00036/0302).

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 Pronamel Toothpaste and Sensodyne Enamel-Pro Toothpaste contain 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 and protects against acid erosion.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of using Sensodyne Pronamel Toothpaste and Sensodyne Enamel-Pro Toothpaste outweigh the risks, hence Marketing Authorisations have been granted.

SENSODYNE PRONAMEL TOOTHPASTE
SENSODYNE ENAMEL-PRO TOOTHPASTE

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SCIENTIFIC DISCUSSION

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INTRODUCTION

These Marketing Authorisation applications are submitted under Article 8.3(i) of Directive 2001/83/EC (as amended), for a known active substance. Sensodyne Pronamel Toothpaste and Sensodyne Enamel-Pro Toothpaste are considered to be line extensions 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 Dentrifice 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. Fluoride also protects against acid erosion by promoting the tooth remineralisation/rehardening and inhibiting tooth demineralisation/enamel softening.

These products are identical (apart from the product names) and are white, mint flavoured toothpastes, containing 5% w/w potassium nitrate and 0.32% w/w sodium fluoride. These products will be available without prescription and can be bought from pharmacies and other outlets.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Sodium fluoride

INN name: Sodium Fluoride
Other names: Natrii Fluoridum, Natrium Fluoratum
Molecular formula: NaF Relative Molecular Weight: 41.99
Physical form: A white powder or colourless crystals

A satisfactory description of the manufacturing process for sodium fluoride is provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

As the sodium fluoride used in the manufacture of the toothpaste is tested in accordance with the requirements of the Ph. Eur, no validation data is needed.

Batch analysis results are provided in the form of Certificates of Analysis (CoA) which state compliance with the Ph. Eur. (4th Edition).

The purity of sodium fluoride is determined a commercially sourced titrant.

A satisfactory specification for the packaging that comes into direct contact with sodium fluoride has been provided, confirming that the packaging complies with food contact regulations. A declaration from the manufacturer is provided confirming compliance with Directive 2002/72/EC.

Satisfactory stability data are presented that support the proposed retest period.

Potassium nitrate

INN name: Potassium Nitrate
Other names: Kalii nitras
Molecular formula: KNO_3 Relative Molecular Weight: 101.10
Physical form: A white crystalline powder, white granules or colourless crystals.

A satisfactory description of the manufacturing process for potassium nitrate is provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

As the potassium nitrate used in the manufacture of the toothpaste is tested in accordance with the requirements of the Ph. Eur, no validation data is needed.

Batch analysis results are provided in the form of Certificates of Analysis (CoA) which state compliance with the Ph. Eur.

The manufacturer uses a USP and National Institute for Standards and Technologies (NIST) reference standard for the assay of the potassium nitrate.

A satisfactory specification for the packaging that comes into contact with potassium nitrate has been provided, confirming that the packaging complies with food contact regulations.

Satisfactory stability data are presented that support the proposed retest period.

DRUG PRODUCT

Composition

The qualitative composition of Sensodyne Pronamel Toothpaste and Sensodyne Enamel-Pro Toothpaste is as follows:

Ingredient Name	**Reference to Standard**
Active Ingredients	
Potassium Nitrate	Ph Eur
Sodium Fluoride	Ph Eur
Excipients	
Purified Water	Ph Eur
Sorbitol, Liquid 70% (Non crystallising)	Ph Eur
Glycerol	Ph Eur
Silica, Dental Type (Amorphous)	Ph Eur
Silica, Dental Type (Hydrated)	Ph Eur
Macrogol (Polyethylene Glycol 300)	Ph Eur
Cocamidopropyl Betaine	HSE
Flavour Blend 10926	HSE
Xanthan Gum	Ph Eur
Saccharin Sodium	Ph Eur
Titanium Dioxide	Ph Eur

Sodium Hydroxide	Ph Eur

There are no overages used in the manufacture of this product.

All the excipients except cocamidopropyl betaine and the Flavour blend 10926 have a Ph. Eur. monograph, and are tested according to Ph. Eur. methods. Cocamidopropyl betaine and the Flavour blend 10926 are tested to a satisfactory specification. Copies of Certificates of Analysis (CoA) for the excipients have been provided by the suppliers.

There are no raw materials derived from animals used in these products, therefore none of the materials used pose a risk of transmission with respect to TSE or BSE.

Manufacture
A satisfactory description of the manufacturing method has been provided.

As there are no intermediate manufacturing steps no specific point at which in-process controls have been applied. The bulk product is analysed in accordance with the finished product specification.

No process validation data has been provided. It is stated that the manufacturing process is a conventional method used in the industry. The finished product manufacturer has committed to perform full scale validation on the first three commercial batches of the licensed product manufactured at the proposed site and will notify the MHRA in the event of any unexpected results. An acceptable process validation scheme has been provided.

Finished product specification
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 analyses data are presented and are acceptable. There is little inter-batch variation.

Container closure system
The toothpaste is filled into plastic barrier laminate tubes. The 45, 75 and 100 ml pack will be fitted with a tamper evident foil seal and a colour cap whilst the 20 ml pack is fitted with a colour cap and no foil seal.

Detailed descriptions of the primary packaging are provided. Specifications for the materials of the primary packaging system are also provided, along with written declarations from packaging suppliers stating that all the components are compliant with food contact regulations for immediate packaging (Directive 2002/72/EC, except for the 20ml laminates which comply with EC Directive 90/128).

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results a shelf-life of 2 years has been set, provided the

product is stored below 30 ºC. In-use stability data was also generated, which supported a shelf life of 6 months once the container has been opened.

Bioequivalence / bioavailability

No clinical studies were performed on the toothpastes. As this is a topical preparation, this is not required by the guidelines.

Product literature

The SPCs for these products are satisfactory. The carton has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the carton information is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Assessor's overall conclusions

Granting of Marketing Authorisations is acceptable.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT REPORT

INTRODUCTION

Indications
The indications for these products are for the relief of dentinal hypersensitivity, prevention of dental caries and protection against the effects of acid erosion of tooth enamel.

Dose and dose regimen
The products are for dental use and are to be used 2-4 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 these products.

Bioequivalence
No bioavailability or bioequivalence studies have been conducted on these products.

CLINICAL EFFICACY
The combination of potassium nitrate and sodium fluoride in anti-caries/anti-sensitivity toothpaste is not novel. No specific clinical studies were conducted to investigate the efficacy of the proposed products for the proposed indications of anti-caries or anti-sensitivity because there is extensive literature which demonstrates that fluoridated toothpastes significantly decrease the incidence of dental caries and that fluoridated potassium nitrate toothpastes reduce dental sensitivity.

CLINICAL SAFETY
Formulations similar to the proposed products 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 Pronamel Toothpaste and Sensodyne Enamel-Pro Toothpaste are safe for their intended use and are 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.

EXPERT REPORTS

A comprehensive clinical overview and biopharmaceutical summary for the proposed products have been provided by the manufacturer. This appropriately addresses the areas of clinical pharmacology, efficacy, safety and benefit/risk relevant to the proposed product.

PRODUCT LITERATURE

SPC

It is noted that there are two SPCs, both for identical formulations of toothpaste but under two distinct product names - Sensodyne Pronamel Toothpaste and Sensodyne Enamel-Pro Toothpaste.

Patient Information Leaflet

Label

Information for patients is supplied on the product cartons. The information for patients is clear and readable.

RISK BENEFIT

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

CONCLUSION

These products can be granted Marketing Authorisations.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of the products 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 applications 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 these applications.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit ratio is considered to be positive.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 9 November 2005
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 10 November 2005
3	Following assessment of the application the MHRA requested information relating to the quality dossier on 2 February 2006 and the clinical dossier on 17 May 2006
4	The applicant responded to the MHRA's requests, providing further information the quality dossier on 6 November 2006
5	Following assessment of the response the MHRA requested further information relating to the quality dossier on 26 January 2007
6	The applicant responded to the MHRA's request, providing further information on the quality dossier on 14 June 2007 and the clinical dossier on 15 June 2007
7	Following assessment of the response the MHRA requested further information relating to the quality dossier on 19 July 2007 and the clinical dossier on 27 July 2007
8	The applicant responded to the MHRA's request, providing further information on the quality and clinical dossiers on 30 October 2007
9	A Marketing Authorisation was granted on 27 November 2007

SUMMARY OF PRODUCT CHARACTERISTICS

PL 00036/0105:

1 NAME OF THE MEDICINAL PRODUCT

Sensodyne Pronamel Toothpaste

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Potassium Nitrate 5.0% w/w
Sodium Fluoride 0.315% w/w (1450 ppm fluoride)
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Toothpaste
Smooth, glossy slightly milky/transluscent white to cream paste at pH 7.1

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of dentinal hypersensitivity
Prevention of dental caries
Protection against the effects of acid erosion of tooth enamel

4.2 Posology and method of administration

For dental use
Use 2-4 times a day, in place of ordinary toothpaste

4.3 Contraindications

Known allergic reactions 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
Potassium ions are thought to reduce hypersensitivity by interfering with pulpal nerve conduction.
Sodium fluoride is an established anticaries agent, which prevents dental caries. Fluoride inhibits caries and acid-erosion of dental enamel and dentine by promoting tooth remineralisation/rehardening and inhibiting tooth demineralisation/enamel softening. Fluoride in the oral cavity is incorporated into hydroxyapatite in enamel to form fluoroapatite. Fluoroapatite is less soluble than hydoxyapatite and more resistant to acid attack than the original enamel that it replaces. Fluoride also inhibits the metabolism of acid-producing bacteria which are responsible for caries.
Dental type silicas act as polishing and cleaning agents to assist in the removal of food remnants from the teeth. The grade of silica in the product provides an abrasivity level which is low relative to most other toothpastes, but is within that recommended in the International Standard ISO 11609 for dentifrice products.

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

Purified Water,
Sorbitol, Liquid (non-crystallising),
Silica, Dental Type,
Glycerol,
Macrogols,
Xanthan Gum,
Titanium Dioxide (E171),
Cocamidopropyl Betaine,
Saccharin Sodium,
Sodium Hydroxide,
Mint Flavour 10926.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 Years
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:

Pack Type	Pack Size (ml)
Decorated polyethylene barrier laminate tube with a tamper evident foil seal and a colour cap	45, 75, 100
Polyethylene barrier laminate tube with a colour cap	20

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special precautions.

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 00036/0105

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/11/2007

10 DATE OF REVISION OF THE TEXT

27/11/2007

PL 00036/0302:

1 NAME OF THE MEDICINAL PRODUCT

Sensodyne Enamel-Pro Toothpaste

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Potassium Nitrate 5.0% w/w
Sodium Fluoride 0.315% w/w (1450 ppm fluoride)
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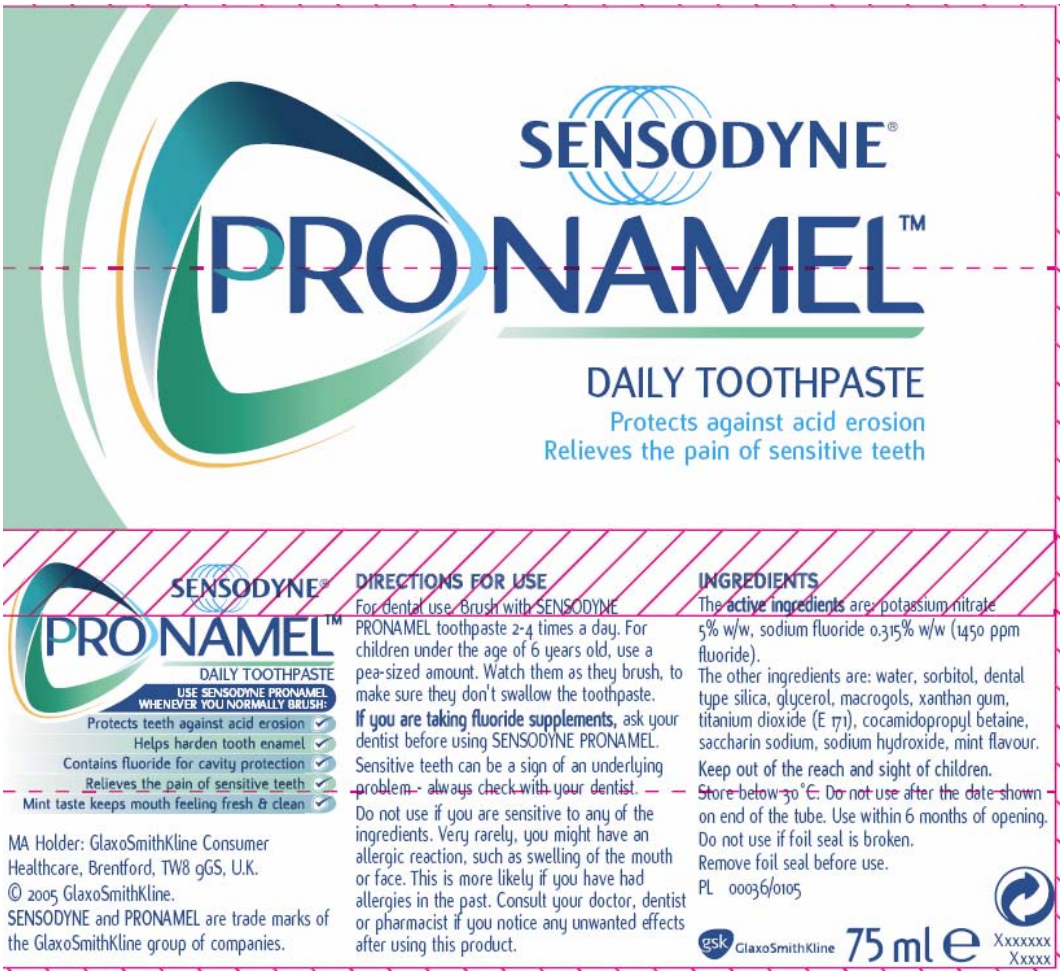
10 DATE OF REVISION OF THE TEXT
27/11/2007

LABELLING-PATIENT INFORMATION

PL 00036/0105

Label:



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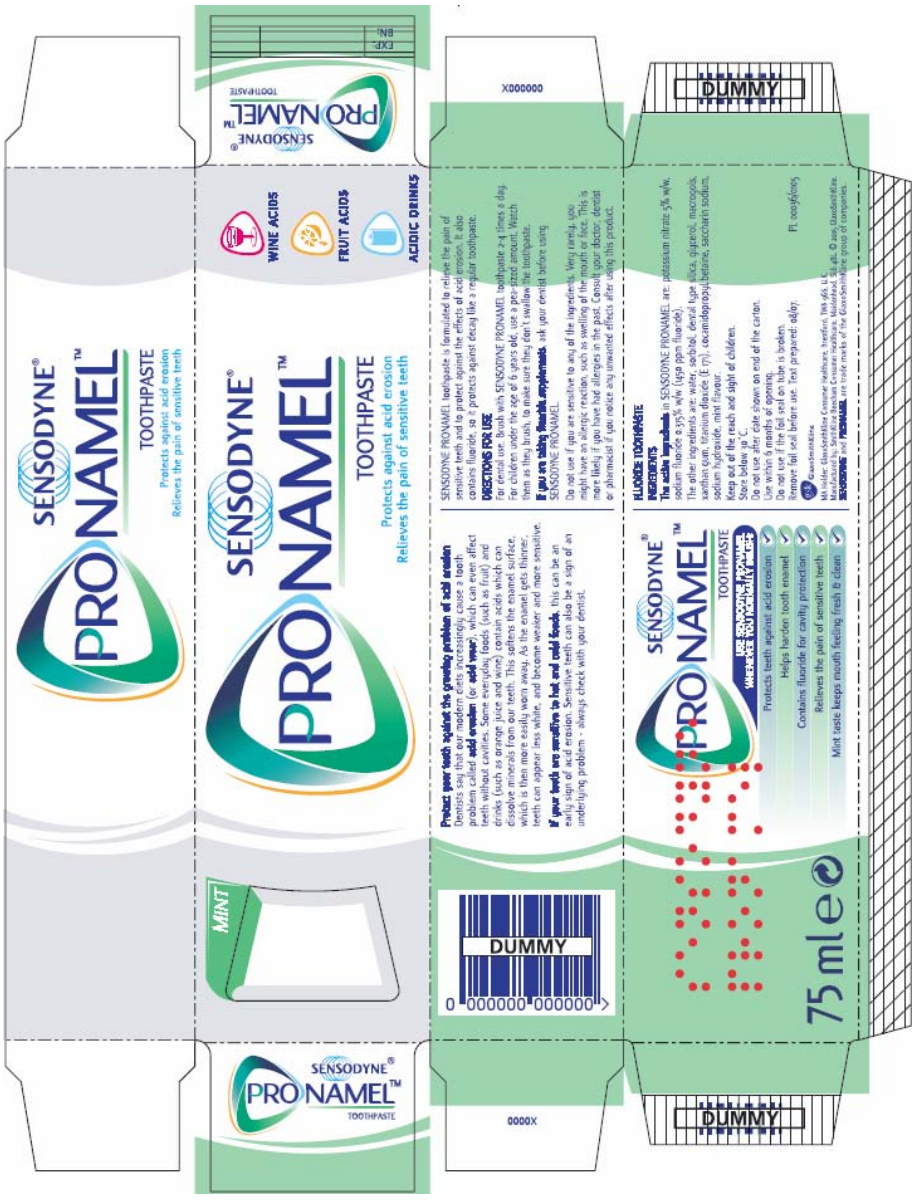
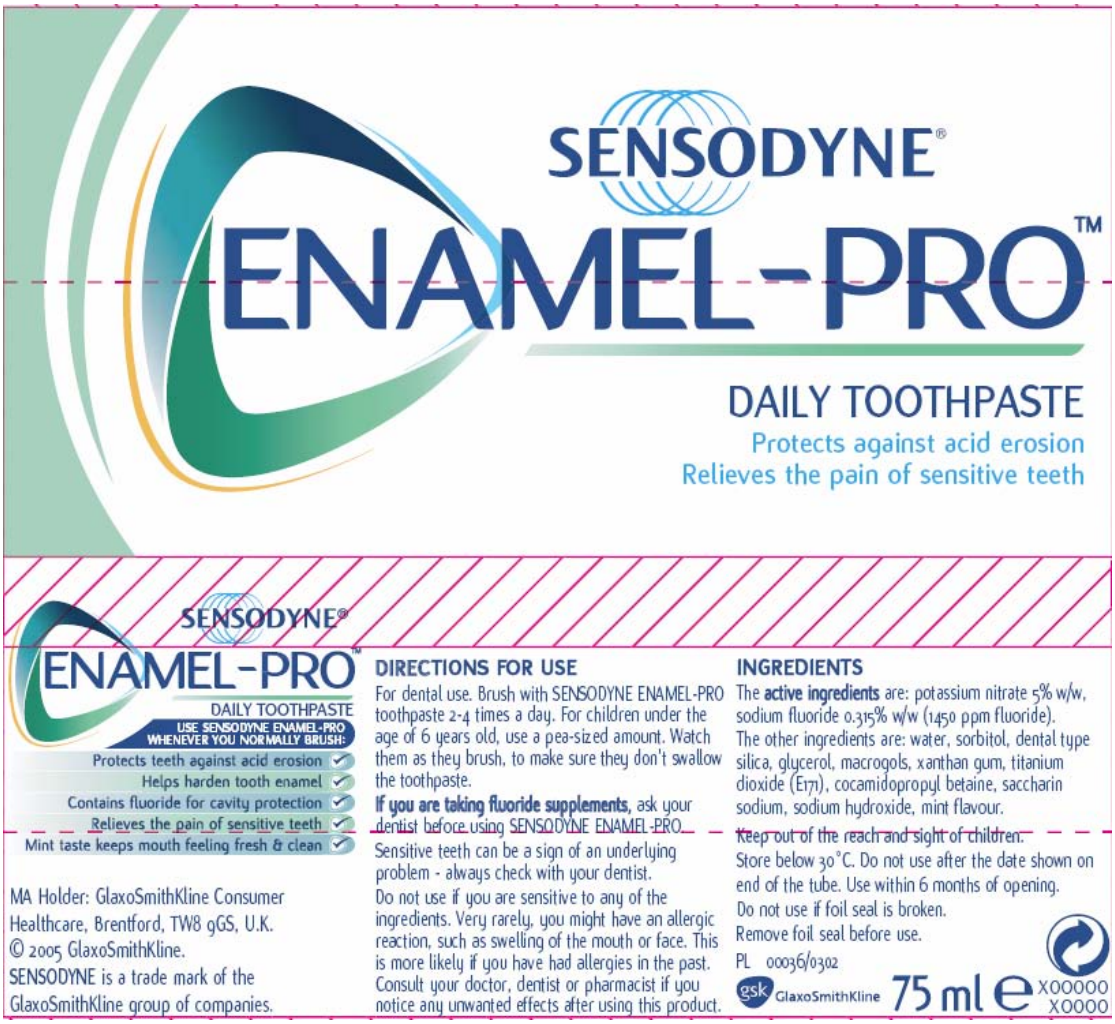

SENSODYNE®
PRONAMEL™
TOOTHPASTE
Protects against acid erosion
Relieves the pain of sensitive teeth
WINE ACIDS
FRUIT ACIDS
ACIDIC DRINKS
MINT
DUMMY
75 ml e

PL 00036/0302

Label:



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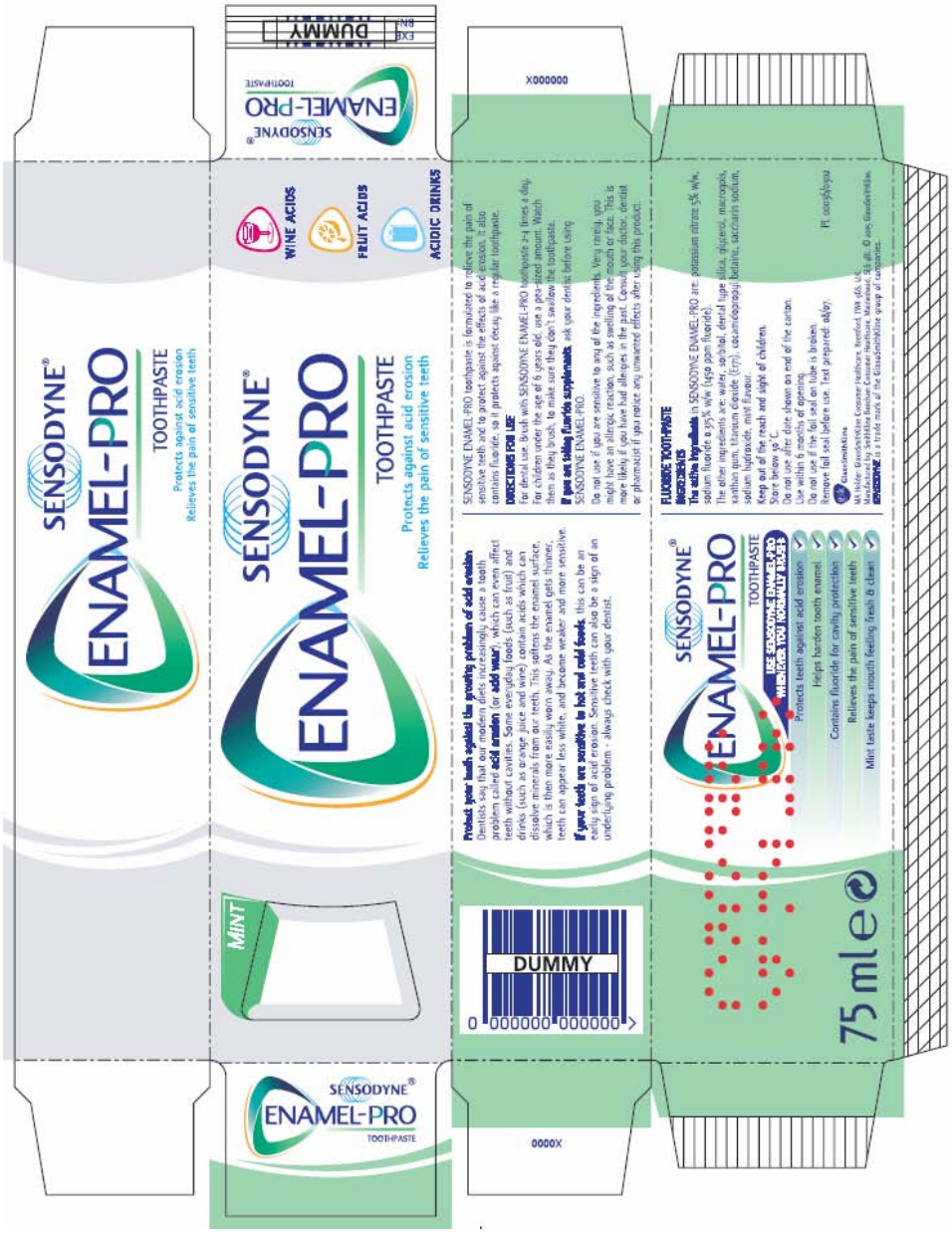
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