Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Sodium Fluoride 2800 ppm Toothpaste
Sodium Fluoride 5000 ppm Toothpaste

(sodium fluoride)

PL 30684/0271-0272

DAWA Limited

LAY SUMMARY
Sodium Fluoride 2800 ppm Toothpaste
Sodium Fluoride 5000 ppm Toothpaste
(sodium fluoride)

This is a summary of the Public Assessment Report (PAR) for Sodium Fluoride 2800 and 5000 ppm Toothpaste. It explains how these products 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 these products.

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

What is Sodium Fluoride 2800 and 5000 ppm Toothpaste and what are they used for?
These applications are for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Sodium Fluoride 2800 ppm Toothpaste is used to treat and help prevent dental caries (tooth decay) in children aged 10 years and over and adults, particularly amongst patients at risk from multiple caries.

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

How do Sodium Fluoride 2800 and 5000 ppm Toothpaste work?
This toothpaste contains fluoride as sodium salt, which belongs to a group of medicines called caries preventing agents. When Sodium Fluoride 2800 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 Sodium Fluoride 2800 and 5000 ppm Toothpaste used?
The pharmaceutical form of these medicines is a toothpaste and the route of administration is for application to the teeth (topical).

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

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

How to use Sodium Fluoride 2800 ppm Toothpaste (persons aged 10 years and older):
Use daily instead of the normal toothpaste.
Brush carefully and thoroughly, for one minute, morning and evening:

- apply a 1 cm ribbon of toothpaste onto the toothbrush for each brushing
- brush teeth vertically, from the gum to the tip of the teeth
- careful brushing takes approximately one minute
- spit out excess foam and do not swallow

- for best results do not drink or rinse for 30 minutes.

How to use Sodium Fluoride 5000 ppm Toothpaste (persons aged 16 years and older):
The patient should use Sodium Fluoride 5000 ppm Toothpaste 3 times a day for brushing their teeth:

- apply a 2 cm ribbon onto the toothbrush for each brushing (2 cm provides between 3 mg and 5 mg of fluoride)
- brush the teeth after each meal
- vertically, from the gum to the tip of the tooth
- spit out excess foam and do not swallow.

Careful brushing takes approximately 3 minutes.

For further information on how Sodium Fluoride 2800 and 5000 ppm Toothpaste are used, refer to the package leaflet and Summaries of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Sodium Fluoride 2800 and 5000 ppm Toothpaste have been shown in studies?
As the active substance sodium fluoride has been in clinical use for over 10 years, data were provided in the form of literature references to show that:

- Sodium Fluoride 2800 ppm Toothpaste is a safe and efficacious treatment to help prevent dental caries (tooth decay) in children aged 10 years and over and adults, particularly amongst patients at risk from multiple caries.

and

- Sodium Fluoride 5000 ppm Toothpaste is a safe and efficacious treatment to help prevent dental caries (tooth decay) in adolescents aged 16 years and over and adults, particularly amongst patients at risk from multiple caries.

What are the possible side effects of Sodium Fluoride 2800 and 5000 ppm Toothpaste?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflet or the SmPC available on the MHRA website.

Why was Sodium Fluoride 2800 and 5000 ppm Toothpaste approved?
It was concluded that the data provided from literature references had shown that Sodium Fluoride 2800 and 5000 ppm Toothpaste is effective in the treatment of the afore-mentioned indications. Furthermore, use of the active substance sodium fluoride in the European Union has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Sodium Fluoride 2800 and 5000 ppm Toothpaste?
A Risk Management Plan (RMP) has been developed to ensure that Sodium Fluoride 2800 and 5000 ppm Toothpaste is used as safely as possible. Based on this plan, safety information has

been included in the SmPC and the package leaflet, 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 and reviewed continuously.

Other information about Sodium Fluoride 2800 and 5000 ppm Toothpaste
Marketing Authorisations for Sodium Fluoride 2800 and 5000 ppm Toothpaste were granted in the UK on 27 January 2021.

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

This summary was last updated in March 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Sodium Fluoride 2800 and 5000 ppm Toothpaste (PL 30684/0271-0272) could be approved.

The products are approved for the following indications:
Sodium Fluoride 2800 ppm Toothpaste:

- For the prevention and treatment of dental caries (coronal and root) for adolescents and children aged over 10 years old.

Sodium Fluoride 5000 ppm Toothpaste:

- Prevention of dental caries in adolescents and adults, particularly amongst patients at risk from multiple caries (coronal and / or root caries).

The primary mode of the caries preventative action of fluoride is post eruptive, i.e. topical. Systemic fluoride supplements are believed to act also mainly topically (e.g. during ingestion, via saliva).

There are three types of effect associated with fluoride:

- The inhibiting effect on demineralisation (lowering the enamel solubility in an acid environment);
- The promotion of remineralisation of enamel during the caries process;
- A bactericidal effect upon dental plaque organisms. This inhibits the proliferation of dental plaque bacteria and prevents formation of the acids that cause caries.

Fluoride alone is not enough to eliminate bacterial plaque, nor as a complete treatment for caries.

These applications were submitted under Article 10a of Directive 2001/83/EC, as amended, (regulation 54 of The Human Medicines Regulation 2012, as amended) as well-established use applications. No new non-clinical or clinical studies were submitted, as the data submitted for these applications is in the form of literature references.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 21 March 2019 and 18-19 June 2020 who on the evidence before them had reason to think that on grounds relating to quality, safety and efficacy, they might be unable to advise the grant of these applications. In response to the CHM advice, the applicant provided further data to address these concerns. The information provided was adequate and the issues were resolved, and Marketing Authorisations were granted for these products on 27 January 2021.

II QUALITY ASPECTS

II.1 Introduction

1 g of toothpaste contains 2.8 or 5 mg fluoride (as sodium fluoride) corresponding to 2800 ppm fluoride, (sodium fluoride 0.619% w/w) or 5000 ppm fluoride (sodium fluoride 1.1%w/w).

In addition to sodium fluoride, these products also contain the excipients:
Sodium Fluoride 2800 ppm Toothpaste:
Glycerol, sodium benzoate (E211), sorbitol solution (70 per cent) (non-crystallising), precipitated silica (MFIL P), precipitated silica (ABSIL 100), macrogol 600, sodium lauryl sulphate, carmellose sodium (DVPS), flavour mint FLV 8020 (propylene glycol), titanium dioxide (E171), saccharin sodium and purified water.

Sodium Fluoride 5000 ppm Toothpaste:
Sodium benzoate (E211), tetra potassium pyrophosphate, sorbitol solution (70 per cent) (non-crystallising), precipitate silica (MFIL P), precipitate silica (ABSIL 100), macrogol 600, carmellose sodium (DVPS), sodium lauryl sulphate, saccharin sodium, brilliant blue FCF (E133), flavour spearmint No. 1 (propylene glycol), flavour mint FLV 8020 (propylene glycol)and purified water.

Sodium Fluoride 2800 ppm Toothpaste:
75 ml of toothpaste is filled in a white coloured lami tube fitted with white coloured flip top cap enclosed in an outer carton.

Sodium Fluoride 5000 ppm Toothpaste:
51g of toothpaste is filled in a white coloured lami tube fitted with white coloured cap enclosed in an outer carton.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: Sodium fluoride

Chemical Name:	Sodium fluoride
Molecular Formula:	NaF
Molecular Weight:	41.99 g/mol
Appearance:	White or almost white powder or colourless crystals.
Solubility:	Soluble in water, practically insoluble in ethanol (96 per cent).

Sodium fluoride is the subject of a European Pharmacopoeia monograph.

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

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product(s).

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months with the storage conditions 'Do not store above 25ºC', is acceptable. The in-use shelf life of the product is 'once opened use within 6 months.'

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
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
These applications were submitted under Article 10a of Directive 2001/83/EC, as amended (regulation 54 of the Human Medicines Regulations 2012, as amended), a well-established use applications. No new non-clinical studies were submitted, as the data submitted for these applications is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology
The pharmacology of sodium fluoride is well known and adequately described in the applicant's non-clinical overview.

No new data have been submitted and none are required for applications of this type.

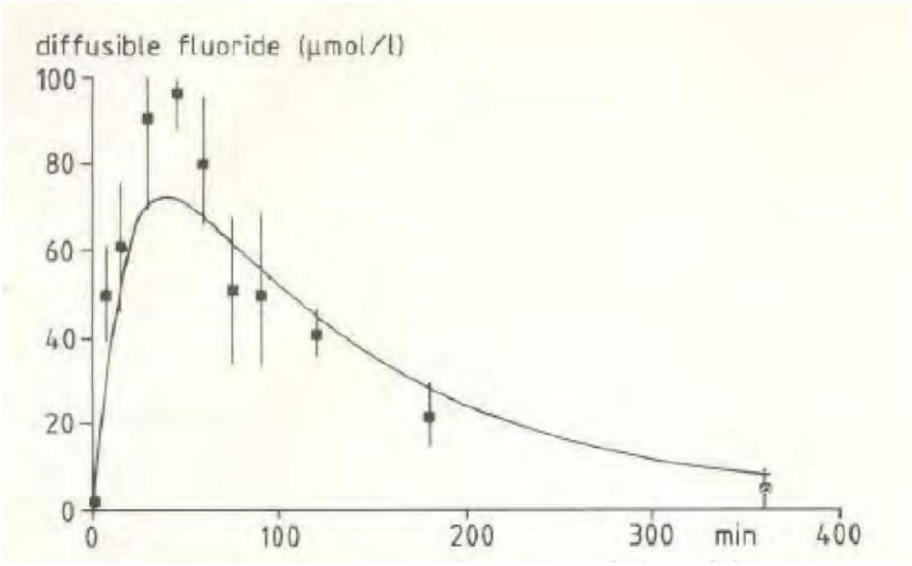
III.3 Pharmacokinetics
Absorption
Plasma and urine samples were collected for 7 h after the IV administration of fluoride (0.5 mg F/kg) to dogs, cats, rabbits, rats and hamsters. Plasma clearance (Cp) ranged from 3.5 to 8.6 mL/min/kg in the dog and hamster, respectively. Renal clearance (Cr) ranged from less than 1.5 mL/min/kg in the dog and rabbit to about 3.5 mL/min/kg in the rat and hamster.

Extra-renal clearances (Cer) ranged from 2.1 mL/min/kg in the dog to over 4.5 mL/min/kg in the cat, rabbit, and hamster. It was concluded that (there are major quantitative differences in the metabolic handling of fluoride among the five species, and that Cp, Cr, and Cer values of the young adult dog, when factored for body weight, resemble those of the young adult human most closely.

Rats (4/group) received 40, 80 or 160 µmol of fluoride/day in 1 ml of water. The greatest AUC was obtained with an oral dose of 80 µmol of NaF. This parameter was significantly greater with 80 µmol than with 40 µmol NaF, but similar to that observed with 160 µmol. Faecal fluoride excretions (in the 24 h following a single dose of NaF) and the bone fluoride contents (found at the end of 30 days of treatment with 40, 80 or 160 µmol NaF/day), agreed with the AUC values. The rate of fluoride absorption (v, µmol/10 min) through the intestinal wall was investigated with perfused, isolated rat duodenum in vivo. Fluoride absorption increased between 0 and 10 mmol/l luminal fluoride and decreased with higher concentrations.

After the administration of an oral dose of 80 µmol of NaF to female rats, the AUC of total plasma fluoride was 10200 µmol.min/l. Absorption of NaF in fasting rats was 99.3 % as inferred from the faecal excretion of 0.66 ± 0.56 µmol/day of fluoride in the 24 h following the oral intake of 80 µmol of NaF. Figure 1 below shows the experimental values of plasma fluoride in the next 360 min after a single oral dose of 80 µmol of NaF to rats; total plasma fluoride does not differ significantly from diffusible plasma fluoride concentration. The urinary excretion of fluoride in the 7 h that follow the oral administration of 80 /lmol of NaF was 6.1 ± 0.7 µmol.

Figure 1:



Fasted 350 g male rats were administered 50 ~g F (as NaF) in either water or a 7.5% pectin solution. Pectin markedly slowed gastric emptying, but by 2 h, more than 90% of the solution had passed into the small intestine in both groups, and F absorption exceeded 90% in both groups. The rate of F absorption was initially much slower in the pectin group than in the group given F in water, and plasma F concentration increased more slowly and reached a lower maximum value. Absorption from the stomach was greater in the pectin group, but still accounted for only approximately 25% of total gastrointestinal absorption. The reduced rate of F absorption and slower rise in plasma F concentration accompanying delayed gastric

emptying indicate that passage of F into the small intestine is the major factor in rapid F absorption.

Plasma fluoride concentrations were studied in 11 pigs following single oral or intravenous doses of fluoride. Animals coded A to F were fed twice daily with a standard diet and those coded G to J were fed twice daily with low calcium diet. Semi-logarithmic plots of fluoride concentration vs. time after i.v. injection of F- (F and J) showed an exponential pattern of the curves.

The plasma half-lives of the two single experiments in a fasting state (code H) were 1.07 and 1.43 h. When the F dose was given together with food (code I), the curves indicated a delayed absorption rate, making it more difficult to estimate a true elimination phase of the curves. For the four animals given 30 or 45 mg F- together with the standard diet (coded D and E), the plasma fluoride curves were inconsistent.

The bioavailability was the same for both diets when fluoride was given in the fasting state (53% - 56%).

When the F dose was given together with food, the bioavailability was reduced to 40% - 42% for the low-calcium diet and was further reduced to 15% - 19% when given with an equivalent quantity of the standard diet.

Three adult ewes were given sodium fluoride solutions at 3 dose levels (0.15, 0.375 and 0.75 mg/kg bw). Blood samples were collected at pre-dose and at 2, 5, 8, 10, 15, 30 min and 1, 1.5, 2, 2.5 and 3 h, and then at hourly intervals until 10 h post injection. After IV administration of sodium fluoride at the 3 tested doses, plasma concentration decreased abruptly between 2 to 15 min and then more slowly.

Comparison of the different parameters indicated an absence of change with dose level, suggesting that fluoride behaved linearly at the doses under study. The half-life of elimination was 2.57 ± 1.28 h, the steady-state volume of distribution was 0.26 ± 0.5 L/kg and the body clearance was 0.105 ± 0.26 L/ kg/h.

Experimental studies performed *in vivo* with rats and *in vitro* with isolated segments of dog jejunum have indicated that fluoride (as sodium fluoride) is rapidly absorbed from the stomach and intestinal tract in animals. The rate at which fluoride is absorbed from the stomach is inversely related to the pH of the stomach contents.

Although most of the fluoride ingested by laboratory animals is absorbed through the gastrointestinal tract, small amounts may also be absorbed from the oral cavity. In female Fischer F-344 rats intubated endotracheally (with oesophageal ligation) with 200 µl of a solution of sodium fluoride ($Na^{18}F$), approximately 7% of the administered material was absorbed from the oral cavity within 2.5 hr. The absorption of fluoride (as sodium fluoride in solution) from the oral cavity of Syrian hamsters increased with decreasing pH of the solution.

In laboratory animals, the presence of food and fluoride binding ions (i.e., aluminium, calcium, magnesium) in the gastrointestinal tract significantly reduces the amount of fluoride absorbed into the general circulation. The absorption of ingested fluoride by female Wistar rats was reduced from 76 to 47% when the level of calcium in their diet was increased from 0.5 to 2%. In male albino rabbits administered drinking water containing 25 or 250 mg

fluoride/litre (as sodium fluoride) for 4 weeks, the levels of fluoride in the serum (and femoral bone) were approximately 2-fold higher in animals administered a diet low in calcium (0.4%) than in controls administered a diet containing 1.6% calcium.

Fluoride (F) is readily absorbed from the small intestine. In many epithelia, F transport appears to occur predominantly as the weak acid HF. For the same mechanism to exist in intestinal epithelium, with the high pH of the intestinal lumen (and thus low proportion of HF), the discrimination in favour of HF vs F would have to exceed 10^4:1. F was added to the mucosal buffer (0.1–1.0 mM F) and mucosal to serosal F transfer was measured after 30 minutes. F transfer was proportional to mucosal F concentration but was found not to be pH dependent within the range pH 6.0–8.0. F transfer was strongly affected by changing the transmural potential difference (by substitution of Cl^- and Na^+, and by ouabain inhibition). The data indicate that intestinal F passage occurs predominantly as the anion F rather than the weak acid HF.

The rate of F absorption from the stomach is pH-dependent, with greater absorption at low pH. Since the rate of absorption is also strongly influenced by the rapidity of gastric emptying. Male rats (350 g, n = 85) were pre-treated with cimetidine (to inhibit gastric acid secretion) or pentagastrin (to stimulate gastric acid secretion) or were untreated controls, and given 50 µg F by stomach intubation. The pH of the F-containing solution was varied in the cimetidine-pre-treated group (pH 1.5, 5.5, 8.5), and was 5.5 for the control and pentagastrin-pre-treated groups. The rate of gastric emptying was unaffected by pre-treatment or pH of the intubating solution. Initially, F absorption was greatest at low pH. After 40 min, absorption was comparable in all groups, averaging approximately 70% of the initial dose. The extent of absorption from the stomach was inversely related to pH, but increased absorption from the small intestine compensated for the low gastric absorption at high pH.

Distribution

The rate of clearance of fluoride from plasma by bone is higher than that of calcium. In laboratory animals, approximately 99% of the total body burden of fluoride is retained in bones and teeth, with the remainder distributed in highly vascularised soft tissues and the blood. The degree to which fluoride is stored in the skeletal tissue is related to the turnover rate of skeletal components and the level of previous exposure.

Metabolism

The metabolism of fluoride in animals is similar to that of humans.

The 40-day metabolism of the animals receiving sodium fluoride, sodium silicofluoride and stannous fluoride is reported in table below. There does not appear to be any marked difference in the amount of fluorine in the faeces of any of the various groups nor in the urinary fluorine level of the silicofluoride and the sodium fluoride group. Previous data, obtained by determining fluorine storage alone, have suggested that various inorganic ions interfere with the metabolism of fluorine in the rat.

TOTAL FLUORINE METABOLISM

SUPPLEMENT	TOTAL INGESTED (MG. F PER RAT)	TOTAL EXCRETED	
		URINE (MG. F PER RAT)	FECES (MG. F PER RAT)
Sodium fluoride	1.26	0.59	0.13
Sodium silicofluoride	1.28	0.55	0.14
Stannous fluoride	1.27	0.48	0.12

The effects of ingestion of sodium fluoride (NaF), 10 mg/kg body weight for 50 days, on the structure and metabolism of sperm of albino rats were investigated. In different groups of rats, the reversible effects upon withdrawal of NaF treatment and by administering some therapeutic agents, viz., ascorbic acid and calcium alone and in combination with NaF (50 and 70 days), on sperm structure and metabolism were also studied. The results revealed that the sperm acrosomal hyaluronidase and acrosin were reduced after 50 days of NaF treatment. Sperm stained with acidic alcoholic silver nitrate revealed acrosomal damage and deflagellation, which might be causative factors for the reduced activity of the enzymes. These alterations also resulted in a decline in sperm motility. The cauda epididymal sperm count was decreased, perhaps because of spermatogenic arrest. Thus, the low sperm motility and count ultimately contributed toward reduction in fertility by NaF treatment. However, withdrawal of NaF treatment for 70 days produced incomplete recovery, while administration of ascorbic acid and calcium, individually and in combination, brought about significant recovery of fluoride-induced effects. Thus, the effects of fluoride on sperm structure and metabolism of rats are transient and reversible.

Excretion

A number of pharmacokinetic parameters (i.e., plasma, renal and extrarenal clearances) in mongrel dogs, Sprague-Dawley rats, cats, rabbits and hamsters intravenously administered a single dose (0.5 mg fluoride/kg body weight) of sodium fluoride and concluded that dogs most resembled humans with respect to their elimination of fluoride; plasma clearance rates were approximately 2-fold higher in rats than in dogs.

Plasma clearance of fluoride in rapidly growing domestic pigs ranged from less than 1.5 to over 8 ml/min/kg, depending on the ages of the pigs, while values of 3-4 mL/min/kg were reported for the young adult dog.

Pharmacokinetic drug interactions

After injection with sodium fluoride, animals were immediately treated with injections of sodium chloride (control), calcium chloride (low- or high dose), or magnesium sulfate. The major outcome was 6-hour survival using a Cox Proportional Hazard model. All untreated animals died within 60 minutes. Using a Cox Proportional Hazard model, each 1.8 mM/kg dose of calcium chloride administered reduced the risk of death by 33%. Magnesium sulfate treatment was not associated with a hazard reduction. Calcium chloride administered simultaneously with sodium fluoride reduces the bioavailability of fluoride poisoning in a mouse model. The equivalent dose of magnesium sulfate does not significantly decrease fluoride bioavailability.

Rabbits (n = 10) were orally administered an aqueous solution of 10 mg NaF/kg daily for 18 months. The fasting plasma calcium concentrations of fluoride-treated rabbits were significantly lower than those of control animals. In contrast to the decrease in plasma calcium level, an increase in intestinal radioactive calcium (^{45}Ca) absorption was observed in all fluoride-treated animals. However, urinary calcium excretion levels were found to be

reduced in fluoride-treated rabbits. It is therefore concluded that long-term fluoride poisoning alters the calcium homeostatic mechanism, thereby affecting calcium metabolism.

III.4 Toxicology

The LD_{50} values for sodium fluoride in the mouse, hamster, rabbit, and rat spanned a five-fold range of from 46 to 250 mg/kg (21 to 113 mg F/kg) which might be due, at least in part, to species differences in fluoride metabolism. The intravenous LD_{50} in mice was 23.0 + 0.9 mg/kg and the oral LD_{50}, 46.0 + 1.6 mg/kg. Acute toxicity studies in mice conclude that kidneys are adversely affected by prolonged use of sodium fluoride.

The effect of chronic and acute exposure to sodium fluoride (5, 10, 20, and 50 mg/kg body weight/day) for fifteen weeks on hepatic damage in young albino rabbits revealed increasing degrees of hepatocellular necrosis, degenerative changes, hepatic hyperplasia, extensive vacuolisation in hepatocytes, and centrilobular necrosis in the liver of the exposed animals.

Fluoride intake in high doses has toxic effects on various organs. Chronic fluorosis results in tubular degenerations, inflammation, fibrosis, parenchymatous nephritis, cloudy swellings, and dilations of convoluted tubules. In addition to these effects, fluoride causes deteriorative effects on the skeleton, teeth, and soft tissues. Histopathological disorders were observed on the slides prepared from the liver specimens of the animals exposed to chronic fluorosis depending on doses of chemicals given to the animals. Hyperaemia, local necrosis, hydropic degeneration, vacuolar degenerations, and swelling on hepatocytes around the central vein were detected.

Colloidal chitosan – silver nanoparticle – fluoride nanocomposites are potential options for the control of multiple-drug-resistant microorganisms and do not represent substantial risks to human health. The cytotoxicity was dependent on F concentration and exposure time. Sodium fluoride was negative for gene mutation induction in Salmonella typhimurium strains TA100, TA1535, TA1537, and TA98 with and without S9. Studies in animals have shown that following oral administration of sodium fluoride to mice, rats and rabbits, reproductive and feto-toxic effects were observed only at high dose levels. Fluoride hampers the reproductive functions of male rabbits and is proportional to the duration of fluoride exposure whereas exposure of female rats to sodium fluoride (200, 400 and 600 ppm NaF) in drinking water has adverse fetotoxic effects.

Female reproductive function is inhibited by NaF and that exposure to NaF causes ovarian and uterine structural damage. NaF may thus significantly reduce the fertility of female rats. NaF reduces sperm motility, capacitation, and the acrosome reaction leading to poor fertilisation and suppressed embryonic development.

Conflicting results have been reported concerning the genotoxicity of NaF. Studies focusing on possible genotoxic effect of excess fluoride are contradictory. According to some authors, fluoride does not induce DNA damage however some have observed the genotoxic potential. In genotoxicity study in mice, NaF induced different types of chromosome aberrations which were found to be dose-dependent. Repeated fractionated dosing (chronic) produced less aberrations than that of the acute dose. It seems reasonable that NaF is a potent mutagen in the *in vivo* experimental situations reported and hence restricted exposure in humans is suggested.

Additionally, in another *in vitro* study, NaF at concentration ranging from 7 to 100 µg/ mL did not contribute to DNA damage and was not considered as genotoxic.

Mice studies did not reveal any significant increase in the frequency of cytogenetic damage in mice after long-term administration of high concentrations of NaF and did not produce any DNA strand breaks in testicular cells at doses 84 mg/kg. NaF at high dose promotes dental fluorosis, but does not induce DNA breakage in leukocytes, oral mucosa and brain cells in rats. In a comprehensive assessment of genotoxicity, sodium fluoride was evaluated in a battery of cellular tests providing different genetic end points and biotransformation capabilities. Negative findings were made in all assays, indicating that sodium fluoride is not genotoxic in these assays

Whereas in mouse model study; NaF exhibited genotoxic activity and enhanced oxidative damage.

These findings are clinically important since they represent an important contribution to a correct evaluation of the potential health risk associated with the exposure to dental agents. Genotoxicity tests constitute an important part of cancer research for risk assessment of potential carcinogens. The findings hereby reported represent a valuable contribution for evaluation of the potential health risk associated with NaF use in dental practice. The applicant's drug product is used as oral toothpaste and no portion of the drug is to be swallowed. Hence, it is unlikely that the genotoxic effects reported in experimental conditions can bring any cause of clinical concerns in humans following oral use at doses recommended in the SmPC.

Toxicology conclusion
The available non-clinical information suggests that sodium fluoride has a safety pharmacology and toxicity profile that will not preclude its clinical use according to the restrictions addressed in the SmPC. The characteristics of sodium fluoride are adequately reflected in the SmPC and the indications and precautions for the use of this drug are justified by its pharmacological properties. The benefit risk profile of sodium fluoride is considered to be favourable, provided that the product is used according to the SmPC. Overall, it can be stated that the investigations performed on sodium fluoride cover all aspects of safety assessment required and can therefore demonstrate an acceptable level of safety for sodium fluoride under the conditions stipulated in the SmPC.

III.5 Ecotoxicity/Environmental Risk Assessment
An Environmental Risk Assessment (ERA) has been provided. The results of the ERA show that there is no risk of increased environmental exposure with the use of these products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
No new clinical studies were submitted, as the data submitted for these applications is in the form of literature references. The literature review provided is satisfactory.

IV. 2 Pharmacokinetics (PK)
The pharmacokinetics of sodium fluoride are well established. Sodium fluoride toothpaste has a local, topical action on teeth and is not intended to be swallowed. Minimal systemic exposure is therefore expected.

A comprehensive summary of the pharmacokinetics of fluoride has been presented, including aspects of absorption, influence of food, distribution, metabolism, elimination, the effects of impaired renal function, age, PK in special populations and interactions. The applicant has also provided suitable bridging data demonstrating comparability between their product and the bibliography. For example, the applicant has provided a comparison of the formulation of the proposed products for marketing and those of Duraphat 2800 ppm and 5000 ppm Fluoride Toothpaste, which is claimed to demonstrate the similarity between the formulations. It is considered that adequate justification has been provided to 'bridge' the proposed products to the established Duraphat products. Therefore, literature concerning the safety and efficacy of Duraphat 5000 ppm Fluoride Toothpaste can be directly applied as supporting evidence in the application for the proposed product.

IV.3 Pharmacodynamics

Sodium fluoride applied topically after tooth eruption reduces caries by inhibiting demineralisation and promoting remineralisation of the tooth surface. It is effective on both enamel and exposed dentine.

The primary mode of the caries preventative action of fluoride is post-eruptive, i.e. topical. Systemic fluoride supplements are believed to act also mainly topically (e.g. during ingestion, via saliva). There are three types of effect associated with fluoride:

- the inhibiting effect on demineralisation (lowering the enamel solubility in an acid environment);
- the promotion of remineralisation of enamel during the caries process;
- A bactericidal effect upon dental plaque organisms. This inhibits the proliferation of dental plaque bacteria and prevents formation of the acids that cause caries.

The fluoride ion (F) has been widely used topically in the treatment of dental caries for its anticariogenic and antimicrobial properties. The antibacterial action of fluoride is due to the acidification of the bacterial cytoplasm through the formation of H^+ and F^- ions from hydrogen fluoride and the disruption the bacterial metabolism by inhibition of vital bacterial enzymes such as proton releasing adenosine triphosphatase and enolase.

A pilot study was performed to evaluate in situ the effect of F toothpaste, at a concentration of 1100 μg F/g, on dentine demineralisation. This pilot study was approved by the research and Ethics Committee of the Piracicaba Dental School. A double blind, crossover design study was conducted in two phases of 14 days each, during which six volunteers wore palatal appliances containing four slabs of bovine root dentine with known surface hardness. For this study six volunteers (21–35 years old), who fulfilled inclusion criteria (normal salivary flow rate, good general and oral health with no active caries lesions or periodontal treatment needs, ability to comply with the experimental protocol, not having used antibiotics during the 2 months prior to the study and not using fixed or removable orthodontic devices) were selected to participate in the study. A 10% sucrose solution, prepared by the researchers, was provided for the volunteers. This solution was applied extra-orally to the slabs eight times per day as a cariogenic challenge. The volunteers brushed their teeth and the appliance with a non-F toothpaste (negative control) or F toothpaste (1100 μg F/g, NaF/silica-based) three times a day (the dentifrice formulations were prepared by Colgate/Palmolive, São Bernardo do Campo, Brazil). On the 10th and 14th days of each phase, two slabs were collected and evaluated for mineral loss by SH. The sequence of toothpaste used by each volunteer was randomly assigned and, after the two phases, all volunteers had undergone the two

treatments. From the above study it was observed that the effect of the dentifrice factor was significant ($p < 0.001$), showing lower % SHL for the group treated with F toothpaste (42.0± 9.7) compared with the control (62.0±6.4) group. However, the effect of time was not significant ($p > 0.05$). From the above study it was concluded that F toothpaste at 1100 µg F/g is able to decrease dentine caries even under a high cariogenic challenge of biofilm accumulation and sugar exposure.

A study was performed to investigate the effect of four different toothpastes with differing fluoride compounds on enamel remineralisation. For this study a 3 × 3 mm window on the enamel surface of 90 human premolars was demineralised in a hydroxyethylcellulose solution at pH 4.8. The teeth were divided into 6 groups and the lower half of the window was covered with varnish serving as control. The teeth were immersed in a toothpaste slurry containing: placebo tooth paste (group 1); remineralisation solution (group 2); Elmex Anticaries (group 3); Elmex Sensitive (group 4); Blend-a-med Complete (group 5) and Colgate GRF (group 6). Ten teeth of each group were used for the determination of the F-content in the superficial enamel layer and acid solubility of enamel expressed in soluble phosphorus. Of 6 teeth of each group serial sections were cut and investigated with polarisation light microscopy (PLM) and quantitative energy dispersive X-ray analysis (EDX). From the above study the PLM results showed an increased remineralisation of the lesion body in the Elmex Anticaries, Elmex Sensitive and Colgate GRF group but not in the Blend-a-med group. A statistically significant higher Ca content was found in the Elmex Anticaries group. The fluoride content in the superficial enamel layer was significantly increased in both Elmex groups and the Blend-a-med group. Phosphorus solubility was significantly decreased in both Elmex groups and the Blend-a-med group. From the above study it was concluded that the amine fluoride compounds in toothpastes result in a clearly marked remineralisation of caries like enamel lesions followed by sodium fluoride and sodium monofluorophosphate formulations.

IV.4 Clinical efficacy

The use of fluoridated toothpastes has been demonstrated to have a caries reduction efficacy 25% greater than that for non-fluoridated toothpastes.

Dose-response relationship

There is a well-established dose-response relationship between the concentration of fluoride present in dentifrices and caries prevention and the evidence to support the use of fluoridated toothpastes is described by one review as unequivocal. A recent review examined the use of fluoride toothpastes containing up to 2,800 ppm and described a dose-response effect to this level but stated that this was not always statistically significant between individual concentrations. The review found that the highest probability of caries preventive benefits was found in those toothpastes containing greater fluoride concentrations. In previous comparisons with placebos, low concentrations (400–550 ppm) demonstrated no significant benefit (and hence should not be recommended for use), with those with ‘standard’ levels of fluoride having a median preventive fraction of 25% and those with the highest levels of fluoride (2,800 ppm) a preventive fraction of 45%. A meta-analysis of 6 randomised clinical trials, examining fluoride concentrations of 1,700, 2,200 and 2,800 ppm, found that the use of a paste containing 2,800 ppm resulted in ‘statistically significant lower caries increment than the use of a dentifrice with 1,100 ppm. While the systematic reviews demonstrate good levels of support for dentifrices up to 2,800 ppm, there is a lack of contemporary clinical trial data (suitable for meta analyses) regarding the use of 5,000 ppm in younger patients. This is important as 2,800 ppm is available in only a small number of markets, leaving 5,000 ppm as the only alternative to consumer brands. There is a strong evidence base for the use of high

fluoride toothpastes in groups at a greater risk of caries. The decision on the concentration of fluoride will be based on a number of factors. A thorough risk assessment of the patient is required prior to the prescription of such therapeutics and it is important to re-assess risk on a regular basis to determine whether the intervention is still required. Early studies on 5,000 ppm suggest that they may have a role to play in addressing the burden of disease in hard-to-reach groups.

Main bibliographic studies

A collaboration review of the effectiveness of fluoride toothpastes in preventing dental caries gave the prevented fraction, pooled from over 42,000 children in the 70 studies included, as 24%. A recent systematic review identified eight trials involving primary teeth and reported caries reductions similar to those recorded for permanent teeth. The ability of fluoride-containing toothpastes to prevent caries in the roots (dentine and cementum) of teeth has been tested in a number of trials and with several compounds, with encouraging results. There is a dose response for fluoride in many vehicles, including toothpaste. The prevented fractions for various fluoride concentrations in toothpastes, taken from a recent review are given in table below:

Fluoride concentration (ppm)	Prevented fraction (%; 5% confidence interval)
250	9.1 (-3.6, 22.0)
440-550	15.4 (-1.9, 32.5)
1000-1250	23.0 (19.3, 26.6)
1450-1500	29.3 (21.2, 37.5)
1700-2200	33.7 (16.5, 50.8)
2400-2800	35.5 (27.2, 43.6)

The higher the concentration of fluoride, the greater the effect. There has been considerable discussion about the effectiveness of toothpastes containing less than 1000 ppm. For toothpastes containing about 500 ppm, it can be seen that the 95% confidence interval includes zero, indicating that the prevented fraction (15.4%) is not statistically significantly different from zero at the 5% level of significance.

Hence, the age group chosen for 2 proposed concentrations (> 10 years of age for the 2800 ppm and > 16 years of age for the 5000 ppm) is appropriate and well acceptable based on literature references, meta-analysis considering the efficacy, safety and risk benefit ratio to the patient in both the considered age groups and also is in line with approved drug products for marketing authorisation holder.

A summary of randomised clinical trials on fluoride concentration in toothpastes showed a positive dose response: pastes with 1,000-1,500 ppm F gave 23% caries reduction compared to fluoride free placebo, this value increased to 36% for pastes at around 2,500 ppm. For pastes below 1,000 ppm no significant difference with placebo was found, probably due to the small number of studies.

Efficacy for 2800 ppm:

A number of randomised controlled clinical trials (RCTs) have assessed the effectiveness of toothpastes containing 2500−2800 ppm F and the results are summarised in the following Table.

Table: Caries increments in studies that have assessed the effectiveness of dentrifrices containing 2500 2800 ppm F (each row represents one study)

Duration years	Age at BL	Fluoride	Conc	Increment	% diff	Significance
3	7–15	NaF NaF	1100 2800	4.40 3.88	 12	 Sig
3	10–13	NaF/MFP NaF/MFP	1000 2500	3.63 3.67		NS
3	11–14	MFP MFP MFP	1000 1500 2500	6.83 6.27 5.56	 8 18	 Sig
3	6–14	MFP MFP	1500 2500	4.23 3.77	 11	 Sig
2	11–14	MFP MFP	1000 2500	5.47 4.96	 9	 Sig
2	9–12	NaF NaF NaF NaF	1100 2800 1100 2800	A 6.27 5.45 B 4.95 3.80	 13 23	 Sig Sig

Studies that have demonstrated the efficacy of fluoride toothpaste in preventing and controlling dental caries include all of the essential features of well conducted clinical trials. These include randomised groups, double blind designs, placebo controls, and meticulous procedural protocols. Taken together, the trials on fluoride toothpaste provide solid evidence that fluoride is efficacious in controlling caries. The quality of evidence for toothpaste is Grade I. Studies of 2 – 3 years duration have reported that fluoride toothpaste reduces caries experience among children by a median of 15% - 30%. This reduction is modest compared with the effect of water fluoridation, but water fluoridation studies usually measured lifetime rather than a few years' exposure. Regular lifetime use of fluoride toothpaste likely provides ongoing benefits that might approach those of fluoridated water. Combined use of fluoride toothpaste and fluoridated water offers protection above either used alone.

Clinical trials outside the United States have reported that toothpaste containing 250 ppm fluoride is less effective than toothpaste containing 1,000 ppm fluoride in preventing dental caries. However, toothpaste containing 500 – 550 ppm fluoride might be almost as efficacious as that containing 1,000 ppm fluoride. A British study reported that the prevalence of diffuse enamel opacities (an indicator of mild enamel fluorosis) in the upper anterior incisors was substantially lower among children who used toothpaste containing 550 ppm fluoride than among those who used toothpaste containing 1,050 ppm fluoride.

Comparisons were made of the clinical effectiveness of two small groups of fluoride containing toothpastes on the basis of published and unpublished information available to the group. One comparison showed that particular sodium fluoride/silica and stannous fluoride/calcium pyrophosphate formulations were effective in reducing the incidence of dental caries in school children and that the former toothpaste was more effective than the latter. A separate comparison showed that certain toothpastes containing sodium mono fluoro-phosphate formulated with either an alumina or an insoluble meta-phosphate abrasive were also effective in reducing and controlling caries. The group recommended that there was a need for additional field trials in which direct comparisons could be made between a wide variety of formulations, and that further research should be carried out to develop improved formulations. Extension of the use of adequately formulated fluoride-containing toothpastes is recommended as a valuable public health measure to reduce the incidence of dental caries.

Toothpastes and mouth rinses are just two of many ways of providing fluoride for the prevention of dental caries. In 1960s, research indicated that fluoride could be successfully incorporated into toothpastes and clinical trials demonstrated their effectiveness. By the end of the 1970s, almost all toothpastes contained fluoride. The widespread use of fluoride-containing toothpastes is thought to be the main reason for much improved oral health in

many countries. Of the many fluoride compounds investigated, sodium fluoride, with a compatible abrasive, is the most popular, although amine fluorides are used widely in Europe. Concentrations of fluoride (F), commonly found, are 1500 ppm (1500 µg F/g) for toothpastes and 225 ppm (225 µg F/ml) for mouthrinse. Several systematic reviews have concluded that fluoride-containing toothpastes and mouthrinses are effective, and that there is added benefit from their use with other fluoride delivery methods such as water fluoridation. From the above study it was concluded that Fluoride toothpastes and mouthrinses have been developed and extensive testing has demonstrated that they are effective and their use should be encouraged.

The caries-prophylactic effect of locally applied fluoride compounds has been emphasised in numerous systematic review articles. Daily use of fluoride toothpaste forms the foundation of caries prophylaxis with fluorides, as it is readily available and, when used regularly, continually provides fluoride ions for caries-protective processes on the tooth's surface. This caries prophylactic effect is evident in all age groups and increases with increasing fluoride concentration. Several studies have shown that children's toothpastes with a fluoride content of 500 ppm are also effective in terms of preventing caries. Especially in countries where other means of fluoridation are implemented (e. g., table salt, drinking water), only children's toothpaste should be used in children up to age 6 in order to prevent fluorosis caused by excess fluoride ingestion. Effect of fluoride toothpaste increases with more frequent tooth brushing. In addition, professionally applied fluoride compounds, such as varnishes or gels, are recommended especially where the caries risk is high. Applied four times per year, this contributes to an improved caries-preventive effect.

Fluoride gels can also be individually brushed on once a week. Systematic reviews show that this reduces caries to a similar extent as quarterly application by a dental professional. Fluoridated mouthwashes should first be given to children when they are old enough for school, and then only if an increased caries risk exists. A randomised, prospective, clinical study also showed that the supervised use of fluoridated mouthwashes in adolescents led to a lower incidence of caries in the approximal area compared to a control group. Studies from the 1990s found 20% more caries in those who rinsed thoroughly after brushing than in those who used other rinsing methods.

The concentration of fluoride in toothpaste is an important determinant of efficacy. Clinical trials indicate that within the range 1,000 to 2,500 ppm F an increase in fluoride of around 500 ppm results in an additional 6% reduction in dental caries. In the UK 41% of the parents of young children aged 1 to 2 years claim to use toothpaste containing less than 600 ppm F. Toothpastes containing higher concentrations of fluoride confer greater protection against dental caries but increase the risk of fluorosis. In contrast, low fluoride toothpastes provide less protection against dental caries but reduce the risk of fluorosis. They may therefore be appropriate for young children if considered to be at low caries risk.

A study was performed to compare the effectiveness of toothpaste containing 440 ppmF (Colgate 0-6 Gel) with one containing 1450 ppmF (Colgate Great Regular Flavour) in reducing caries. For this study a randomised controlled parallel group clinical trial was performed. Dental examinations were conducted under blind conditions but as 'off the shelf' toothpaste (without over wrapping or repackaging) was delivered to the participants, subjects and their families were aware of which toothpaste they were using. This randomised controlled trial assessed the effect of supplying free fluoride toothpaste regularly to children from the age of 12 months to 51/2 years. For this study 7,422 children born in 3-month birth cohorts living in high caries areas in nine health districts in north west England. Within each

district children were randomly assigned to test or control groups.

From the above study it was observed that 3,731 children who were examined and remained in the programme showed the mean DMFT (Decayed, Missing, and Filled Teeth) to be 2.15 for the group who had received 1450 ppmF toothpaste and 2.49 for the 440 ppmF group. The mean DMFT for the control group was 2.57. This 16% reduction between the 1450 ppmF and control group was statistically significant ($P<0.05$). The difference between the 440 ppmF group and control was not significant. Further analyses to estimate the population effect of the programme also confirmed this relationship. From the above study it was concluded that 1450 ppmF provides significant clinical benefit for high caries risk children living and the toothpaste containing 440 ppmF did not provide a significant benefit in these high caries risk communities.

A study was performed to evaluate the changes in the enamel surface microhardness following the continuous demineralisation and application of various types of dentifrices with and without fluoride. For this study the surface microhardness of 12 enamel blocks was checked using Vickers Microindentor. The microhardness was checked at 4 different phases. Enamel specimens were treated with 4 different type of dentifrices and microhardness was checked at the end of tenth day and twentieth day. The collected data was analysed using a statistical software program.

From the above study it was observed that there was an increase in the surface microhardness of all the enamel specimens treated with different dentifrices but the difference was not statistically significant. Among the four dentifrices Stannous Fluoride had an enhanced effect on the surface microhardness (SMH) of enamel. The results were found to be in accordance with the study conducted by another author who suggested that the stabilised stannous fluoride/ sodium hexametaphosphate dentifrice may provide enhanced anticaries performance relative to a Sodium fluoride control dentifrice.

Sodium fluoride, sodium monofluorophosphate and stannous fluoride, all three fluorides help prevent caries by remineralising tooth enamel and protecting against demineralisation. Increase in enamel micro hardness after application of sodium fluoride may be related to the reaction of fluoride ion with enamel surface that resulted in the formation of fluoride containing compounds mainly calcium fluoride. From the above study it was concluded that the dentifrices can increase protection of dental enamel against erosive challenges and dental caries by increasing the surface microhardness of the enamel and providing a remineralising effect.

A study was performed to observe the effectiveness of fluoride supplements in preventing caries and their association with dental fluorosis. For this study the reports evaluated dosage schedules similar to that recommended by the American Dental Association. One potentially highly biased study of primary teeth of children during the first three years of life reported a 47.2 percent reduction in dental caries experience. Investigators in one trial involving 3- to 6-year-old children found a 43.0 percent difference, and another trial of children in this age group did not find a significant benefit. Researchers in several studies involving older children detected a significant reduction in caries increments in permanent teeth with the use of fluoride supplements. Fifteen of the studies had withdrawal rates of 30 percent or higher. All of the five included studies that evaluated the association between use of fluoride supplements and dental fluorosis found that use of the supplements increased the risk of mild-to-moderate fluorosis. From the above study it was concluded that the use of fluoride supplements prevents dental caries in primary teeth. There is evidence that such supplements

prevent caries in permanent teeth. Mild to moderate dental fluorosis is a significant side effect.
Fluoride toothpastes are the most widely used form of fluoride delivery and have been shown to be effective anticaries agents based on several systematic quantitative evaluations, including a review and a Technology Assessment in Health Care review, which provide the highest standard of evidence. In a meta-analysis of 70 trials on the effectiveness of fluoride toothpaste for the prevention of dental caries in children compared with placebo, it was reported that the use of fluoride toothpastes has a caries-inhibiting effect [average reduction in DMFS (Decayed, Missing, Filled Surfaces) of 24% (95% CI, 21% to 28%)] on the permanent dentition. Based on 74 trials involving DMFS scores in the mixed or permanent dentition, the caries-preventive effect of fluoride toothpaste was 23% for 1000/1055/1100/1250 ppmF and 36% for 2400/2500/2800 ppmF; however, toothpastes with 440/500/550 ppmF and below did not show a statistically significant effect compared with placebo. The studies on the deciduous dentition were equivocal. From the above study it was concluded that High-fluoride toothpastes may be indicated for adults at higher risk for developing caries because of the insufficiency of caries control with conventional fluoride toothpaste and/or decreased salivary flow rate. There is some evidence that higher concentration-fluoride toothpaste (5000 ppmF) can help reverse root caries.

A randomised full-crossover sequence clinical study was conducted to evaluate the ability of fluoride in sodium fluoride–silica dentifrice to promote tooth remineralisation and enamel fluoride uptake (EFU), and assess the resistance of the newly formed mineral to attack by dietary acid, across the concentration range used in mass-market dentifrices. Sixty-two healthy subjects were treated with dentifrices containing four different fluoride concentrations: no fluoride; 250 ppm, 1150 ppm and 1426 ppm fluoride. At each treatment visit, under supervision, subjects brushed with 1.5 g dentifrice and rinsed once while wearing the appliance; the appliance was removed after a 4-h remineralisation period and effects on the enamel specimens determined. The primary efficacy variable was surface microhardness recovery (SMHR); others included EFU, relative erosion resistance (RER) and comparative erosion resistance. Highly significant linear and, with the exception of SMHR, quadratic dose–response relationships were observed between all efficacy variables and fluoride concentration. For SMHR, EFU and RER, values for the different fluoride concentrations were statistically resolved from one another, with the exception of the two highest fluoride concentrations. The degree of remineralisation and the acid resistance of enamel after treatment were closely related to EFU. Results suggest that after a single brushing, conventional non-specialised sodium fluoride–silica dentifrices promoted remineralisation of early enamel lesions, and imparted increased acid resistance to the enamel surface, in a dose-dependent manner at least up to 1500 ppm fluoride. This study demonstrated that sodium fluoride, in a conventional nonspecialised dentifrice formulation, can promote repair of the earliest stages of enamel erosion after a single application, in a dose-dependent fashion across the fluoride concentration range used in mass-market dentifrices.

One author presented data from a trial wherein children aged 6–15 years (n = 5,439) were randomised into groups receiving dentifrices containing 1,100, 1,700, 2,200 and 2,800 ppm F. Results after 1 year provided evidence of a positive sodium fluoride dose response. Compared to the 1100 ppm fluoride treatment group, the 1700 ppm fluoride treatment group had an 11.0% reduction in DMFS that was not statistically significant, while the 2200 ppm and 2800 ppm fluoride treatment groups showed statistically significant reductions of 18.6% and 20.4%, respectively. The reductions in caries delivered by the higher fluoride dentifrices were present across all tooth surface types, but were most pronounced for occlusal surfaces. Results at years 2 and 3 were confounded by a concurrent fluoride rinse program, which

involved portions of the study population. While the trends for the higher fluoride dentifrices sodium fluoride dentifrice observed at year 1 remained at years 2 and 3, the difference observed between treatments were substantially less and failed to reach statistical significance. Collectively, the data demonstrate that the 2200 ppm and the 2800 ppm fluoride treatments delivered statistically significantly greater caries efficacy than the 1100 ppm fluoride treatment.

A meta-analysis of 6 randomised clinical trials, examining fluoride concentrations of 1,700, 2,200 and 2,800 ppm found that the use of a paste containing 2,800 ppm resulted in 'statistically significant lower caries increment than the use of a dentifrice with 1,100 ppm.

One article describes a supervised brushing study comparing 2,800 ppm with 1,100 ppm as part of a larger study investigating an experimental stannous fluoride product. As with previous works, statistically significant differences were found between the low, standard and 2,800 ppm groups. Children using the product containing 2,800 ppm experienced a 23.2% reduction (when attending more than 60% of supervised brushing sessions) compared with 1,100 ppm when scored by one examiner, but a much smaller reduction by another – 13%; both, however, were significantly superior to control.

A meta-analysis was performed to determine the relative effectiveness of fluoride toothpastes of different concentrations in preventing dental caries in children and adolescents. Randomised controlled trials and cluster-randomised controlled trials comparing fluoride toothpaste with placebo or fluoride toothpaste of a different concentration in children up to 16 years of age with a follow-up period of at least 1 year were considered. For the 66 studies that contributed to meta-analysis of DMFS in the mixed or permanent dentition, the caries preventive effect of fluoride toothpaste increased significantly with higher fluoride concentrations (DMFS PF compared to placebo 23% (95% credible interval (CrI) 19% to 27%) for 1000/1055/1100/1250 parts per million (ppm) concentrations rising to 36% (95% CrI 27% to 44%) for toothpastes with a concentration of 2400/2500/2800 ppm), but concentrations of 440/500/550 ppm and below showed no statistically significant effect when compared to placebo. This review confirms the benefits of using fluoride toothpaste in preventing caries in children and adolescents when compared to placebo, but only significantly for fluoride concentrations of 1000 ppm and above.

On study group evaluated that toothpastes containing >1,500 ppm fluoride (2,500–2,800 and 5,000 ppm F) provide an additional caries preventive effect on root caries lesions in elderly patients compared to traditional dentifrices (1,000–1,450 ppm F). Available data from the few clinical trials suggest that high-concentration fluoridated toothpaste provides better caries prevention on root caries lesions in the elderly population than traditional F-containing toothpaste.

One author conducted a systematic review to assess the efficacy and safety of fluoride toothpaste use in children younger than 6 years. Use of fluoride toothpaste brushing had a statistically significant effect on mean decayed, missing and filled primary tooth surfaces and decayed, missing and filled primary teeth for populations at high risk of developing caries. The effects of using different fluoride concentration toothpastes on caries varied. Study findings showed either a decrease in the odds of having fluorosis when the use of fluoride toothpaste was initiated after 24 months or no statistically significant difference. The review demonstrates that for children younger than 6 years, fluoride toothpaste use is effective in caries control.

An RCT, which involved children aged 11−14 years, compared toothpastes containing 1000, 1500 and 2500 ppm F. There was a highly significant association between fluoride concentration and caries increment after two and three years. The 2500 ppm F toothpaste delivered an 18% reduction in caries increment compared to the 1000 ppm F toothpaste. The results suggested that, in the range 1000−2500 ppm F, every additional 500 ppm F, over and above 1000 ppm F, would provide a cumulative 6% reduction in caries increment.

Two toothpastes, 1000 and 2500 ppm F, were assessed for their effectiveness in an RCT designed to assess whether, using a number of different diagnostic criteria, the length of clinical studies could be reduced from the conventional 3 years. The study included daily tooth brushing in school and twice daily brushing at home. After one year, the traditional measurement of caries increments indicated no significant difference between the two toothpastes, but after two years there was a 9.3% difference in favour of the 2500 ppm F toothpaste.

As part of an RCT, two sodium fluoride toothpastes, one containing 1100 ppm F the other 2800 ppm F, were compared for two years. Tooth brushing was supervised in school twice a day and ad libitum outside school hours. The two examiners both observed statistically lower caries increments in the groups using the 2800 ppm F toothpaste.

Efficacy for 5000 ppm:
A study was performed to evaluate a dentifrice containing 5,000 ppm F compared to a dentifrice containing 1,450 ppm F in caries-active adolescents. For this study the design was a 2 year, single blind randomised controlled trial and 211 adolescents of 279 (76%) completed the trial. The subjects were divided into two groups and were given one of the assigned F dentifrices for daily unsupervised tooth brushing: (1) Duraphat 5,000 ppm F and (2) Pepsodent Superfluor 1,450 ppm F, both as NaF. The outcome variables were caries incidence and progression of proximal and occlusal caries. The subjects were asked to fill in a questionnaire to evaluate their compliance and they were divided into two subgroups: subgroup A, excellent compliance, and subgroup B, poor compliance. The latter group (28%) comprised the subjects who did not brush twice a day or did not use the dentifrice regularly. Adolescents using 5,000 ppm F toothpaste had significantly lower progression of caries compared to those using 1,450 ppm F toothpaste (A: $p < 0.01$, B: $p < 0.001$), with a prevented fraction of 40%. From the above study it was concluded that subjects using 5000 ppm F toothpaste had significantly lower caries incidence for compliance B compared to those using 1,450 ppm F toothpaste ($p<0.05$); the prevented fraction was 42%.This may indicate that 5,000 ppm F toothpaste has a greater impact on individuals who do not use toothpaste regularly or do not brush twice a day. Thus, 5,000 ppm F toothpaste appears to be an important vehicle for caries prevention and treatment of adolescents with a high caries risk.

A study was performed to test the null hypothesis that there is no difference between the effect of 5000 ppm fluoride toothpaste and 250 ppm fluoride mouth rinse on demineralised human dentin surfaces, against the alternative hypothesis of a difference. One volunteer, with no signs of active caries or periodontal disease, but with moderate previous caries experience (FS = 20) participated in this study. The subject was in good general health and had not taken antibiotics for at least one month. The subject was instructed to use a non-fluoridated toothpaste starting four weeks prior to and continuing throughout the experimental period. The agents being tested in this study were 5000 ppm sodium fluoride (Duraphat, Colgate-Palmolive, Piscataway, New Jersey, USA) and 250 ppm amine fluoride and stannous fluoride (Meridol, GABA, Lörrach, Germany). Specimen without fluoride treatment served as

controls. To account for home-care measures, instead of brushing the appliance with toothpaste, it was immersed in either toothpaste (5000 ppm sodium fluoride) slurry (1:3 w/v toothpaste/water), 10 ml mouth rinse or 10 ml distilled water, according to the experimental group, for 60 seconds once daily. From the above study it was observed that Demineralisation was reflected by mineral loss and lesion depth as measured by microradiography. The data of the lesion depth and mineral loss were normally distributed and presented below.

Table 1: Mineral loss (Vol. % × μm) and lesion depth (μm) of dentin.

Methods	n	Mineral loss (Vol.% × μm)			Lesion depth (μm)		
		Range	Mean	SD	Range	Mean	SD
Control	15	-79.00–483.90	328.56 [a]	137.25	6.70–67.30	19.00 [a]	14.24
250 ppm F	15	151.50–258.10	218.64 [b]	28.40	-14.40–68.70	20.80 [b]	18.10
5000 ppm F	15	-150.80–167.90	60.70 [a, b]	76.35	-29.30–20.10	5.32 [a, b]	11.56

The dentin specimens were exposed for 3 weeks to demineralization and treated with fluoride.
Values with the same superscript ([a, b]) within columns revealed a statistically significant difference ($p < 0.05$).
SD = standard deviation; F = fluoride

The mean mineral loss from dentin was significantly lower in the group treated with 5000 ppm fluoride compared to the 250 ppm fluoride group and the control group. Mineral loss was not found to be statistically significantly different between the 250 ppm fluoride and control groups. The lesion depth in dentin of the 5000 ppm fluoride group was significantly lesser than in the 250 ppm fluoride group and the control group. The lesion depth of the 250 ppm fluoride group and the control group were not found to be statistically significantly different. From the above study it was concluded that treatment of demineralised dentin with toothpaste containing 5000 ppm fluoride may considerably reduce mineral loss and lesion depth on exposed dentin.

A double blind, randomised, parallel group clinical study was performed to compare the dentin tubules occlusion by theobromine---containing dentifrices with (Theodent-classic-F®) and without (Theodent-classic®) fluoride with commercially available standard fluoride (Colgate® Regular) and Novamin® containing (Sensodyne®-5000® - Nupro) dentifrices. Eighty healthy adults (27 males, 53 females) with mean (SD) age of 38.8 (13.9) from different ethnic origins and socio economic status were participated in this study. The subjects were identified with code numbers generated by the data management team, and this number was used for the patient randomisation. After providing informed written consent, subjects underwent a complete intra-oral examination and completed medical and dental history questionnaires. Participants were randomised to one of four commercially available toothpastes (20 participants/ product); theobromine- containing toothpaste without (TC) and with (TCF) fluoride (Theodent classic®), Novamin-containing toothpaste (Sensodyne ®-5000® - Nupro) and standard fluoride toothpaste (Colgate® Regular). All participants received a soft bristled manual toothbrush and their respective toothpaste for use throughout the duration of the study. The 80 subjects recruited for this trial completed the study without any dropout.

From the above study it was observed that there was no incidence of adverse event reported during this study. SEM show increased % COT and % DSL with increasing usage of each product. After 1 and 2 days % COT was significantly ($p<0.05$) higher with Theodent-classic® (TC) and Theodent- classic®-F (TCF) compared with Sensodyne and Colgate. Following 3 and 7 days % COT was not different among TC, TCF and Sensodyne but remained significantly ($p<0.05$) lower in Colgate compared to these three. No difference in % COT between TC and TCF at all measurement points. Within each dentifrice, % COT

increased significantly ($p<0.05$) with increasing usage except in Colgate. At any measurement points, % DSL were significantly ($p<0.05$) higher in TC, TCF and Sensodyne compared with Colgate. Within each dentifrice, % DSL increased with increasing usage but the difference at various measurement points were only significant ($p<0.05$) in Sensodyne and Colgate. From the above study it was concluded that dentin occlusion and smear layer deposition, theobromine-containing toothpaste with and without fluoride were equally more effective in a shorter time period than Novamin®- containing toothpaste; however the three were equally efficacious after one week but not the standard fluoride toothpaste.

A study was performed to evaluate the effectiveness of daily tooth brushing with high-fluoride toothpaste on white spot lesion (WSL) formation in adolescents during treatment with fixed orthodontic appliances (FOA). For this study Four hundred and twenty-four healthy 11- to 16-year-old patients were used and they were randomised to use either toothpaste containing 5000 ppm fluoride or regular toothpaste with 1450 ppm fluoride. Patients allocated to the test group were provided with toothpaste containing 5000 ppm sodium fluoride and instructed to apply 2 cm (approximately 1 g) on the brush and then brush their teeth for 2 min, twice daily, after breakfast and before bedtime, during the period of orthodontic treatment. From the above study it was observed that the use of high-fluoride toothpaste resulted in fewer WSL ($P = 0.042$) with a prevented fraction of 32%. The lateral incisor was most commonly affected in both groups. From the above study it was concluded that daily use of high fluoride toothpaste can significantly reduce the prevalence and incidence of white spot lesions adjacent to fixed orthodontic appliances in adolescents. High fluoride toothpaste should be considered as one of several alternative fluoride supplements for patients subjected to a temporarily increased caries risk.

A single blind, multicentre, parallel, randomised controlled trial was performed to evaluate the effectiveness of the application of high fluoride toothpaste on root caries in adults. Adult patients (n = 130, ♂ = 74, ♀ = 56) from three participating centres, diagnosed with root caries, were randomly allocated into two groups: Test (n = 64, ♂ = 37, ♀ = 27; lesions = 144; intervention: high-fluoride toothpaste with 5000 ppm F), and Control (n = 66, ♂ = 37, ♀ = 29; lesions = 160; intervention: regular-fluoride toothpaste with 1350 ppm F) groups. Clinical examinations and surface hardness scoring of the carious lesions were performed for each subject at specified time intervals (T0 – at baseline before intervention, T1 – at 3 months and T2 – at 6 months after intervention). Mean surface hardness scores (HS) were calculated for each patient. Statistical analyses comprised of two-way analysis of variance and post hoc comparisons using the Bonferroni–Dunn correction.

From the above study it was observed that at T0, there was no statistical difference between the two groups with regard to gender or age and for the overall HS (Test group: HS = 3.4 ± 0.61; Control group: HS = 3.4± 0.66; $P = 0.8757$, unpaired t-test). The ANOVA revealed significantly better HS for the test group than for the control groups (T1: Test group: HS = 2.9 ± 0.67; Control group: HS = 3.1±0.75; T2: Test group: HS = 2.4±0.81; Control group: HS = 2.8±0.79; $P < 0.0001$). However, the interaction term time-point group was not significant. From the above study it was concluded that the application of a high fluoride containing dentifrice (5000 ppm F) in adults, twice daily significantly improves the surface hardness of otherwise untreated root caries lesions when compared with the use of regular fluoride containing (1350 ppm F) toothpastes.

A study was performed to evaluate the influence of the selected marketed toothpastes on the human enamel exposed to acid beverages. For this study Enamel specimens from extracted human teeth were prepared (n = 40). Specimens were randomly divided into 10 experimental

groups, 4 specimens each, which were subjected to acid challenge for 10 min using orange juice (pH 3.79) or Pepsi Cola (pH 2.58) and then immersed for 2 min into a slurry of five marketed toothpastes with distilled water (1 : 3 w/w). The tested toothpastes contained 1450 or 5000 ppm fluoride, CPP-ACP with 900 ppm fluoride, 1450 ppm fluoride with potassium nitrate 5%, all of them as sodium fluoride, and 700 ppm fluoride as amine and sodium fluoride with 3500 ppm $SnCl_2$. Enamel roughness (Ra parameter) by contact profilometer at baseline and after exposure onto soft drinks and slurry was measured. From the above study it was observed that exposure to both beverages caused a similar increase of enamel surface roughness. After the specimens immersion into slurries of toothpastes with 1450 or 5000 ppm fluoride, 1450 ppm fluoride with potassium nitrate 5% and CPP-ACP with 900 ppm fluoride the significant decrease of Ra values were found, reaching the baseline values. However, toothpaste with 700 ppm fluoride and 3500 ppm $SnCl_2$ did not cause any fall in Ra value, probably due to other mechanism of action. From the above study it was concluded that sodium fluoride toothpastes are able to restore the surface profile of enamel exposed shortly to acidic soft drinks.

A study was performed to quantify alterations in the root dentine permeability submitted to treatment with a high fluoride toothpaste and 8% arginine, calcium carbonate, sodium monofluorophosphate toothpaste as a preventive treatment for dentinal tubules exposure followed by acid challenge. For this study the specimens were randomly assigned into 3 groups (n = 10), according to the treatment.

1. Group 1 (Negative Control): Distilled water.
2. Group 2 (5000 F): Duraphat® 5000 toothpaste (Colgate Palmolive – 5000 ppm Fluoride).
3. Group 3 (Arginine): Colgate Pro-Relief® (Colgate Palmolive – 8% arginine, calcium carbonate).

The treatment was performed following the manufacturer instructions. The exposed dentine area was brushed with 3 mg of toothpaste for 1 min (brushed carefully). Duraphat® 5000 toothpaste contains 5 mg of fluoride in 3 mg of toothpaste. After treatment, the specimens were carefully rinsed with distilled water (15 ml). From the above study it was observed that the statistically significant decreasing on dentine permeability after treatment with toothpaste (Friedman test and Dunn's post hoc test). Comparison among groups demonstrated a high increasing on dentine permeability when acid challenge was performed after tooth brushing with distilled water (control group). From the above study it was concluded that tooth brushing associated with a high fluoride or Arginine calcium carbonate toothpaste is able to prevent tooth wear and dentinal tubules exposure *in vitro*. Thus, clinicians must advise patients with risk of erosion or abrasion to brush their teeth before meals and avoid acid drinks intake.

The aim of this article was to report the findings concerning the caries preventive effect of fluoride toothpastes in non- selected populations of various ages with special emphasis on fluoride concentration. The relevant literature was identified by searching the databases using the appropriate search terms. Out of all articles originally identified 54 met the inclusion criteria. The result revealed the strong evidence (level 1) (i) for the caries preventive effect of daily use of fluoride toothpaste compared to placebo in the young permanent dentition (PF 24.9%) (ii) Toothpastes with 1500 ppm of fluoride had a superior preventive effect compared with standard dentifrices with 1000 ppm F in the young permanent dentition (PF 9.7%) and (iii) that higher caries reductions were recorded in studies with supervised tooth brushing compared with non-supervised (PF 23.3%). In conclusion this review reinforced the importance of daily tooth brushing with fluoridated toothpastes for preventing dental caries.

A study was performed to determine the effectiveness and safety of fluoride toothpastes in the prevention of caries in children and to examine factors potentially modifying their effect. A randomised or quasi-randomised controlled trial was performed to compare the fluoride toothpaste with placebo in children up to 16 years during at least 1 year. From the above study it was observed that seventy-four studies were included. For the 70 that contributed data for meta-analysis (involving 42,300 children) the DMFS pooled PF was 24% (95% confidence interval (CI), 21 to 28%; $P < 0.0001$). This means that 1.6 children need to brush with fluoride toothpaste (rather than a non-fluoride toothpaste) to prevent one DMFS in populations with caries increment of 2.6 DMFS per year. In populations with caries increment of 1.1 DMFS per year, 3.7 children will need to use a fluoride toothpaste to avoid one DMFS. There was clear heterogeneity, confirmed statistically ($P < 0.0001$). The effect of fluoride toothpaste increased with higher baseline levels of DMFS, higher fluoride concentration, higher frequency of use, and supervised brushing, but was not influenced by exposure to water fluoridation. From the above study it was concluded that the children who brush their teeth at least once a day with a tooth paste that contains fluoride will have less tooth decay. Tooth decay (dental caries) is painful, expensive to treat and can sometimes lead to serious damage to teeth. Fluoride is a mineral that prevents tooth decay. The review of trials found that children aged 5 to 16 years who used fluoridated toothpaste had fewer decayed, missing and filled permanent teeth after three years (regardless of whether their drinking water was fluoridated). Twice a day use increases the benefit. No conclusion could be reached about the risk that using fluoride toothpastes could mottle teeth (fluorosis), an effect of chronic ingestion of excessive amounts of fluoride when children are young.

A study was performed to investigate the effectiveness of topical fluoride applications in arresting dentin caries. A total of 375 children, 209 boys (56%) and 166 girls (44%) with a mean age of 4.0 years having dentin caries in the upper primary anterior teeth participated in this study. Oral health education was provided to all participants at the beginning of the study and reinforced regularly by the kindergarten teachers. At baseline, one trained dentist examined the children's upper incisors and canines in the kindergartens. The children's parents completed a short questionnaire at baseline and again after 24 months. The questions asked were the child's tooth brushing behaviour and use of fluoride toothpaste, and parental satisfaction with the child's dental appearance and dental health. A total of 308 children attended the 30-month examination, giving an overall drop-out rate of 18%. Intra-examiner reproducibility was very good throughout the study. The values of the Kappa statistic for the duplicate examinations were at least 0.95 for the baseline and follow-up examinations. The mean baseline DMFS score of the upper anterior teeth of the 308 children was 4.66. Their mean number of tooth surfaces with active caries at baseline was 3.92. There were also no statistically significant differences among the five groups of children in any of the above parameters. Slightly more than half (55%) of the 308 children at baseline claimed that they brushed their teeth at least once a day. The majority of the parents, 73%, reported that their children used fluoridated toothpaste. There were no statistically significant differences among the five groups of children in their tooth brushing behaviour or the use of fluoridated toothpaste. From the above study it was concluded that the silver diamine fluoride solution is effective in arresting dentin carries in primary anterior teeth in Chinese preschool children. There is no evidence to support the hypothesis that caries removal prior to the fluoride treatments has an effect on their ability to arrest dentin caries.

A school-based program, utilising supervised brushing with a range of fluoride products (from 1,250 through to 5,000 ppm), was undertaken by one study group. A total of 520 children fully participated in the study and were available for the final examination. There

was a clear relationship between the levels of fluoride in the products and caries preventive fraction, with the group taking products with 5,000 ppm fluoride reporting a 40–45% lower DMFT than those treated with the formulation containing 1,250 ppm fluoride.

One author evaluated the effect of high-fluoride toothpaste (5,000 ppm) compared with a standard dentifrice (1,450 ppm) in caries prevention. Toothpaste slurry with 5,000 ppm F reduced the formation of new dental plaque on tooth surfaces. Caries-active adolescents (14-16-year-olds) using high-fluoride toothpaste during two years had 40% lower progression of caries compared with those using standard toothpaste. Twenty-eight per cent of the adolescents had "poor compliance" and brushed irregularly. Brushing with high-fluoride toothpaste resulted in 42% less new caries lesions among caries-active adolescents with "poor compliance" compared with those with "excellent compliance". Thus, high-fluoride toothpaste is an excellent home care treatment for individuals with high caries risk. Brushing with high-fluoride toothpaste three times a day resulted in almost four times higher F concentration in saliva compared with standard toothpaste twice a day. The retention of fluoride in plaque increased significantly as well. Brushing with 5,000 and 1,450 ppm toothpastes, twice a day plus the "massage" once a day, resulted in the same F concentration in saliva and plaque as brushing 3 times a day with the same paste. High-fluoride toothpaste has a clear role in prevention of dental caries; targeting those at the greatest risk, reducing and arresting caries lesions and thereby reducing the need for operative treatment in caries-active adolescents.

An RCT compared the effectiveness of a toothpaste containing 5000 ppm F with one containing 1100 ppm F in adults with primary root caries. After 3 months, 39 (38%) subjects in the 5000 ppm F group and 9 (11%) in the 1100 ppm F group had one or more lesions that had arrested. After 6 months, 58 (57%) subjects in the 5000 ppm F group and 24 (29%) in the 1100 ppm F group had one or more lesions that had arrested.

On author reviewed the caries-preventive effect of fluoride toothpaste in children. The initial search revealed 179 papers of which 15 met the inclusion criteria. There was strong evidence that daily use of fluoride toothpaste has a significant caries-preventive effect in children compared with placebo (prevented fraction 24%). The effect was boosted by supervised tooth brushing, increased brushing frequency to twice daily, and use of a toothpaste concentration of 1,500 ppm fluoride. There were few studies of high quality reporting findings from the primary dentition. The results reinforced the outstanding role of fluoride toothpaste as an effective caries preventive measure in children.

One review group determined the efficacy of fluoride varnish (5% NaF, Duraphat®, Colgate) added to caregiver counselling to prevent early childhood caries, a two-year randomised, dental-examiner masked clinical trial. Initially, 376 caries-free children were enrolled (mean age ± standard deviation, 1.8 ± 0.6 years). All families received counselling, and children were randomised to the following groups: no fluoride varnish, fluoride varnish once/year, or fluoride varnish twice/year. Intent-to-treat analyses showed a fluoride varnish protective effect in caries incidence. Analysing the number of actual, active fluoride varnish applications received resulted in a dose-response effect. Caries incidence was higher for 'counselling only' vs. 'counselling + fluoride varnish assigned once/year' and 'twice/year'. Fluoride varnish added to caregiver counselling is efficacious in reducing early childhood caries incidence.

IV.5 Clinical safety

The applicant has provided a summary of clinical safety issues, reportedly based upon bibliographic references and available supporting data which reflects the posology.

The safety section of the clinical overview is considered acceptable and includes a safety discussion of the proposed fluoride concentration in the proposed indications and age groups.

Suitable bridging data have also been submitted demonstrating comparability between their proposed product and the products on which the bibliography is based.

No new or unexpected safety concerns were raised from the safety data provided in the literature.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended (regulation 182 of the Humans Medicines Regulations 2012, as amended). The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

The Patient Information Leaflet (PIL)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 (regulation 260(3) of The Human Medicines Regulation 2012, as amended). The results show that the PIL 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.

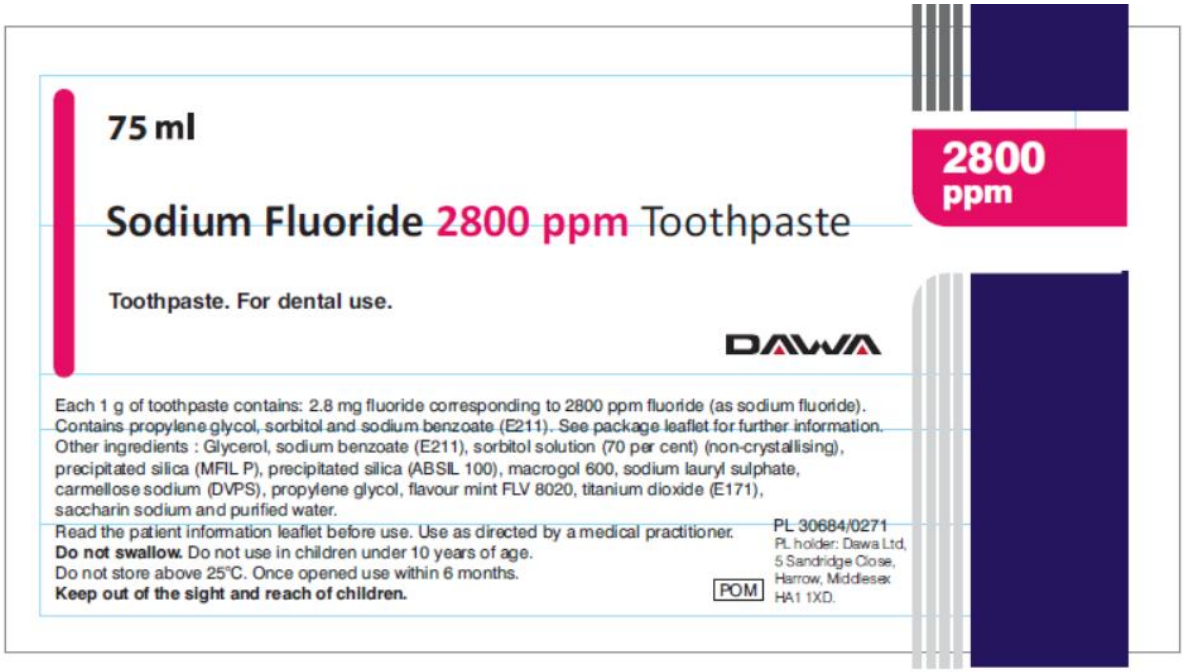
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. 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.

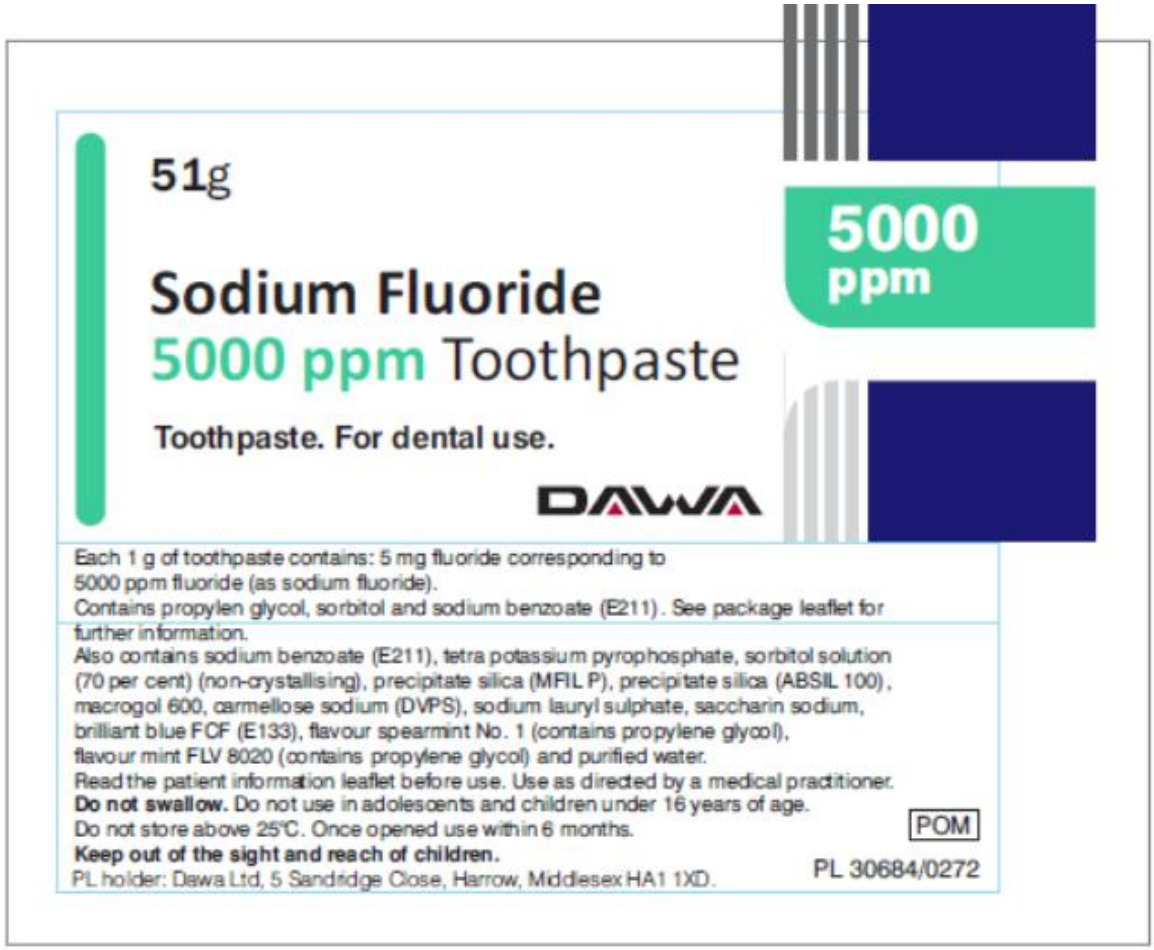
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

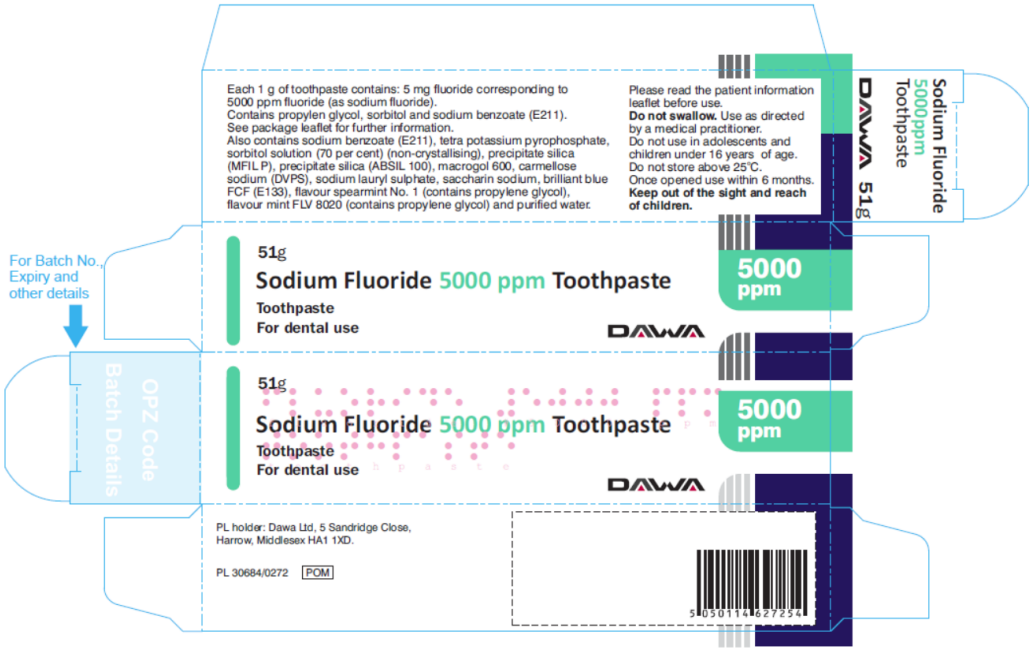
In accordance with Directive 2010/84/EU (regulation 203 of the Human Medicines Regulations 2012, as amended), the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.


75 ml
Sodium Fluoride 2800 ppm Toothpaste
Toothpaste. For dental use.
DAWA
2800 ppm
Each 1 g of toothpaste contains: 2.8 mg fluoride corresponding to 2800 ppm fluoride (as sodium fluoride).
Contains propylene glycol, sorbitol and sodium benzoate (E211). See package leaflet for further information.
Other ingredients : Glycerol, sodium benzoate (E211), sorbitol solution (70 per cent) (non-crystallising), precipitated silica (MFIL P), precipitated silica (ABSIL 100), macrogol 600, sodium lauryl sulphate, carmellose sodium (DVPS), propylene glycol, flavour mint FLV 8020, titanium dioxide (E171), saccharin sodium and purified water.
Read the patient information leaflet before use. Use as directed by a medical practitioner.
Do not swallow. Do not use in children under 10 years of age.
Do not store above 25°C. Once opened use within 6 months.
Keep out of the sight and reach of children.
POM
PL 30684/0271
PL holder: Dawa Ltd, 5 Sandridge Close, Harrow, Middlesex HA1 1XD.


Each 1 g of toothpaste contains: 2.8 mg fluoride corresponding to 2800 ppm fluoride (as sodium fluoride).
Contains propylene glycol, sorbitol and sodium benzoate (E211). See package leaflet for further information.
Other ingredients : Glycerol, sodium benzoate (E211), sorbitol solution (70 per cent) (non-crystallising), precipitated silica (MFIL P), precipitated silica (ABSIL 100), macrogol 600, sodium lauryl sulphate, carmellose sodium (DVPS), propylene glycol, flavour mint FLV 8020, titanium dioxide (E171), saccharin sodium and purified water.
Read the patient information leaflet before use.
Use as directed by a medical practitioner.
Do not swallow.
Do not use in children under 10 years of age.
Do not store above 25°C.
Once opened use within 6 months
Keep out of the sight and reach of children.
DAWA 75 ml
Sodium Fluoride 2800ppm Toothpaste
For Batch No., Expiry and other details
OPZ Code Batch Details
75 ml
Sodium Fluoride 2800 ppm Toothpaste
2800 ppm
DAWA
75 ml
Sodium Fluoride 2800 ppm Toothpaste
Toothpaste. For dental use.
2800 ppm
DAWA
PL holder: Dawa Ltd, 5 Sandridge Close, Harrow, Middlesex HA1 1XD.
PL 30684/0271
POM
DLA


51g
Sodium Fluoride
5000 ppm Toothpaste
Toothpaste. For dental use.
DAWA
5000
ppm
Each 1 g of toothpaste contains: 5 mg fluoride corresponding to 5000 ppm fluoride (as sodium fluoride).
Contains propylen glycol, sorbitol and sodium benzoate (E211). See package leaflet for further information.
Also contains sodium benzoate (E211), tetra potassium pyrophosphate, sorbitol solution (70 per cent) (non-crystallising), precipitate silica (MFIL P), precipitate silica (ABSIL 100), macrogol 600, carmellose sodium (DVPS), sodium lauryl sulphate, saccharin sodium, brilliant blue FCF (E133), flavour spearmint No. 1 (contains propylene glycol), flavour mint FLV 8020 (contains propylene glycol) and purified water.
Read the patient information leaflet before use. Use as directed by a medical practitioner.
Do not swallow. Do not use in adolescents and children under 16 years of age.
Do not store above 25°C. Once opened use within 6 months.
Keep out of the sight and reach of children.
PL holder: Dawa Ltd, 5 Sandridge Close, Harrow, Middlesex HA1 1XD.
POM
PL 30684/0272


Each 1 g of toothpaste contains: 5 mg fluoride corresponding to 5000 ppm fluoride (as sodium fluoride).
Contains propylen glycol, sorbitol and sodium benzoate (E211).
See package leaflet for further information.
Also contains sodium benzoate (E211), tetra potassium pyrophosphate, sorbitol solution (70 per cent) (non-crystallising), precipitate silica (MFIL P), precipitate silica (ABSIL 100), macrogol 600, carmellose sodium (DVPS), sodium lauryl sulphate, saccharin sodium, brilliant blue FCF (E133), flavour spearmint No. 1 (contains propylene glycol), flavour mint FLV 8020 (contains propylene glycol) and purified water.
Please read the patient information leaflet before use.
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Do not use in adolescents and children under 16 years of age.
Do not store above 25°C.
Once opened use within 6 months.
Keep out of the sight and reach of children.
Sodium Fluoride 5000ppm Toothpaste
DAWA 51g
For Batch No., Expiry and other details
QPZ Code Batch Details
51g
Sodium Fluoride 5000 ppm Toothpaste
Toothpaste
For dental use
DAWA
5000 ppm
PL holder: Dawa Ltd, 5 Sandridge Close, Harrow, Middlesex HA1 1XD.
PL 30684/0272
POM

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**