RVG 10942

Ref: [redacted]-37 C

DURAPHAT
(SODIUM FLUORIDE 50 MG/ML SUSPENSION)

PERIODIC SAFETY UPDATE REPORT

VALID FOR THE FOLLOWING MAH:
COLGATE-PALMOLIVE (UK) LTD

PERIOD COVERED BY THIS REPORT: 01.07.2007 – 30.06.2010

~~EU BIRTH DATE: JULY 1968~~

COUNTRIES & REGISTRATION NUMBERS:

THE NETHERLANDS RVG 10942

DATE OF REPORT: **AUGUST 2010**

Prepared by:	
Date: [redacted]	Signature [redacted] C
	Qualified Person Pharmacovigilance, [redacted]
Reviewed by :	
Date: 06 Aug 2010	Signature [redacted] C
	Medical assessor [redacted]

CONTENTS

EXECUTIVE SUMMARY

Duraphat® is a dental suspension containing 50 mg Sodium Fluoride per ml (equivalent to 22.6 mg/ml of Fluoride) indicated for caries prophylaxis treatment or teeth desensitization. In Europe, Duraphat® is a Prescription Only Medicine to be used by a dentist and applied as a thin layer to the dental sites most at risk. In the USA the product is classified as a medical device and is indicated for the treatment of dental hypersensitivity only.

Duraphat® has been acquired by Colgate-Palmolive in 1997 from [redacted] and is marketed internationally by Colgate-Palmolive or a third party.

The current PSUR covers the period from July 2007 up to June 2010 included. Over this period, there have been no suspensions or failure to grant renewal of a Marketing Authorisation for Duraphat®, no change to the formulation of the product and no changes in the target population. Due to an harmonisation of the Summary of Product Characteristics (SmPC) throughout European countries, some changes in the current SmPC have been proposed.

This report confirms that the overall safety profile of Duraphat® Dental Suspension is very good. With an exposure over [redacted] (more than [redacted] doses), there have been fifty-one medically confirmed adverse reaction reports during the period of this PSUR, from which four were classified as serious. For those four serious cases, there is, however, not sufficient evidence to confirm with certainty the causal relationship with the use of Duraphat Varnish as other potential causes were also present or the product was used by a patient for whom the product was contra-indicated.

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Among the 47 non-serious reports, 12 were due to a massive reporting by a same dentist. Six reports only included listed reactions, while in the 41 other reports there was at least one term which was not listed. Apart from the 'application site irritation' which appeared in 12 reports from the same dentist, the most frequent reactions were 'lip swelling' (10 times), 'hypersensitivity' (6 times) and nausea (5 times). All remain, however, at a very low incidence rate when considering an exposure of more than [redacted] patient years.

Overall, the proposed Summary of Product Characteristics contains sufficient information to inform physicians and patients about the occurrence of adverse drug reactions and to warrant the safe use of Duraphat® which still has an excellent risk-benefit ratio when used under the conditions stipulated in the Product Information Leaflet.

1. INTRODUCTION

Duraphat is a dental suspension containing 50 mg Sodium Fluoride per ml, which is equivalent to 22.6 mg/ml of Fluoride.

Duraphat is a dental preparation indicated for Caries prophylaxis in children and adults and for the desensitisation of hypersensitive teeth.

The legal status of the product is a Prescription Only Medicine (POM). In the USA the product is classified as a medical device and is indicated for the treatment of dental hypersensitivity only.

The product is available in several pack sizes, although not all pack sizes are marketed. The pack sizes are 10 ml and 30 ml tubes as well as 1.6 ml ampoules (available in packs of 5).

Colgate-Palmolive acquired the product from [redacted] in May 1997. Since that date applications to transfer the ownership of the Marketing Authorisation have been submitted and approved in Germany, Sweden, Norway, Finland, Denmark, Iceland, Israel, the Netherlands, Australia, New Zealand and Poland. Details of the Marketing Authorisation status are provided in Section 2 below.

The current PSUR covers the period from July 2007 up to June 2010.

MedDRA coding has been performed with MedDRA version 13.0.

2. WORLDWIDE MARKETING AUTHORISATION STATUS

COUNTRY	DATE MA GRANTED	LAUNCH DATE**	TRADE NAME
Germany	10/07/1968*	[redacted]	Duraphat
Belgium	01/06/1975*	NA	Duraphat
Sweden	08/10/1975*	[redacted]	Duraphat
Austria	04/05/1976*	NA	Duraphat
Norway	05/11/1976*	[redacted]	Duraphat
Finland	26/04/1978*	[redacted]	Duraphat
New Zealand	April 1978*	[redacted]	Duraphat
Australia	1978*	[redacted]	Duraphat
Denmark	20/06/1979*	[redacted]	Duraphat
Israel	15/01/1980*	[redacted]	Duraphat
Iceland	26/08/1988*	NA	Duraphat
Netherlands	16/05/1990*	[redacted]	Duraphat
USA	26/07/1995*	[redacted]	Duraphat
Poland	09/07/1997*	NA	Duraphat
UK	06/03/1998	[redacted]	Duraphat

COUNTRY	DATE MA GRANTED	LAUNCH DATE**	TRADE NAME
France	28/03/2000	[redacted]	Duraphat
Greece	24/04/2000		Duraphat
Portugal	16/05/2000		Duraphat
Italy	08/06/2000		Duraphat
Spain	23/01/2002		Duraphat
Switzerland	31/07/2003		Duraphat
Thailand	2003		Duraphat

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* = date of grant of original RPR licence
** = launch date refers to launch of product in Colgate packaging
NA = Not Applicable

3. UPDATE OF REGULATORY AUTHORITY OR MAH ACTIONS TAKEN FOR SAFETY REASONS

There have been no suspensions or failure to grant renewal of a Marketing Authorisation for Duraphat dental suspension. There has been no change to the formulation of the product or changes in the target population.

4. CHANGES TO REFERENCE SAFETY INFORMATION

There have been no significant changes to the clinical indications or the warnings during the period of this PSUR. However, in order to harmonise the Summary of Product Characteristics (SmPC) throughout Europe, a Core Company Safety Information (CCSI) has been prepared. Some modifications to the current SmPC are thus proposed and have been highlighted in red in the attached SmPC.

The CCSI is attached in Appendix 1 and the proposed SmPC in Appendix 2.

5. PATIENT EXPOSURE

The number of units sold is used as a 'bench mark' assessment. The sales data (volume of units sold, July 2007 to June 2010 incl.), and assumptions used to make an estimation are described in Appendix 3.

The estimated patient exposure is [redacted] **doses.** This equates to roughly [redacted] **patient years.**

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Please refer to Appendix 3 for an in-depth analysis.

6. INDIVIDUAL CASE HISTORIES

6.1 General Considerations

All individual case reports meeting the criteria defined below received by Colgate Palmolive during the review period are presented in the line-listings.

- All serious adverse reactions whatever the source of the information (patients, health care professionals, authorities, post-authorisation safety studies, clinical studies and literature)
- Non-serious unlisted adverse reactions from spontaneous reporting (patients, health care professionals, authorities and literature)
- Non-serious listed adverse reactions from spontaneous reporting (patients, health care professionals, authorities)

Adverse events are assessed for:

- Seriousness
- Causality
- Whether listed or unlisted.

The definition of a serious event is one that is fatal, life threatening, results in significant disability or incapacity, results in hospitalisation or prolongs hospitalisation, causes a congenital anomaly/birth defect, is another significant event (i.e. events judged to be medically serious or which are significant by specification in certain trials) or results in the transmission of an infectious agent via the medicinal product. An unlisted event is one whose nature, severity, specificity or outcome is not consistent with the information included in the Core Company Safety Information (CCSI).

6.2 Cases Presented as Line Listing

Line listings of all cases included in the report as explained above are displayed in Appendix 4 (medically confirmed reports) and in Appendix 5 (non medically confirmed patient reports).

6.3 Overview – summary tabulation

In the period under review, there were a total of 51 individual case histories related to the use of Duraphat and reported directly by healthcare professionals and Competent Authorities. Four of them were serious cases and forty-seven were non-serious.
Five spontaneous reports also came directly from the patients without being confirmed by a healthcare professional and are not included in the summary tabulation.

The 51 medically confirmed cases gave rise to a total of 107 terms to describe the symptoms. A summary tabulation of the terms used in the individual case reports is presented in Appendix 6.

Regarding the preferred terms (PTs), one of them was reported 12 times: 'application site irritation'. However, they all came from the same report by a dentist saying that he had approximately 12 patients who had such a reaction. Otherwise, the most frequently reported terms were 'lip swelling' which appeared 10 times, 'hypersensitivity' which appeared 6 times and 'nausea' which appeared 5 times. All other terms were reported only 1 to 4 times with no general trends that could be identified. Regarding the System Organ Classes (SOC), most reports were related to gastrointestinal disorders (24 reports) or to general disorders and administration site conditions (15 reports from which 12 were from the same dentist).

Overall, the adverse reactions mostly concern isolated reports with no particular adverse drug reaction or cluster of adverse drug reaction standing out from the rest.

6.4 Analysis of Individual Case Histories

In this chapter each case is presented according to the most prominent condition, i.e. in descending order: serious unlisted, serious listed, non-serious unlisted, non-serious listed.

6.4.1 Serious Unlisted Reports

In the reporting period of this PSUR four serious unlisted case reports were received.

- The first case was initially reported by [redacted] A follow-up with the 'Dentist Chamber' and with the reporting dentist provided further information.

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• [redacted]	
Source : initial report	[redacted] on 19.03.2009
Source : follow-up report	1) from the Dentist Chamber in [redacted] 2) from the treating dentist on 01.04.2009
Reaction(s)	Dizziness
Short assessment	The case is serious (medically important) according to [redacted] The case is unlisted.
Short narrative:	

Report from [redacted] A dentist reported that a 26-year-old male patient experienced dizziness after use of Duraphat Varnish. The time interval between the start of the product administration and the event was 26 days. The dizziness lasted for 1 week and all day long, but the patient was able to continue working. The patient recovered without any treatment. No further details were provided. ***Follow up Information received from Dentists Chamber in*** [redacted] ***and from the treating dentist***: The product is identified as Duraphat varnish ([redacted]). The product was applied only once by a cotton in the dentists' clinic on 26.2.2009. According to the dentist, dizziness occurred on 26.2.2009 a couple of hours after application. Application time was 3-4 seconds. The mouth was not rinsed after the application. The reaction lasted about 1 week (all day long), but the person could work. The product was applied on a molar and on oral mucosa. The product was used for the first time. Dizziness disappeared without any treatment. The patient usually uses only aminofluoride free toothpastes.
Assessment: As the case has been considered as serious in the [redacted] report due to medical significance, it is also classified as serious by the MAH. Nevertheless, the dentist who initially reported the case does not consider the case as being serious and it is unknown who upgraded the case as serious. The reaction is unlisted. Furthermore, there has not been any medical evaluation of the symptom to exclude any alternative cause (neurological or otolaryngological disease).
Additional Note: The chronology of events between the initial report and the medically confirmed report are not in harmony. The report from [redacted] tated that the time interval between the start of the product administration and the event was 26 days while the dentist stated that the events occurred a few hours after application.

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- The second case was initially reported under the form of an ASPR (Anonymized Single Patient Report) from the [redacted] in the [redacted] with very few details. A consumer reported a similar case to Colgate two weeks later. During the follow-up with the consumer, it was considered that the case was identical to the one reported in the ASPR with sufficient evidence and similarities to link the two reports together.

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• [redacted]	
Source	[redacted] who received the case from a dentist (initial information) Consumer & dentist (follow-up information)
Reactions	Allergic reaction, anaphylactoid reaction, palpitations, weakness, shaking, nervousness, incoherent, lip swelling
Short assessment	The case is serious (medically significant). The case is unlisted.

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Short narrative:	
The case was reported through a yellow card to [redacted] on 29 Dec 2008 and Colgate was made aware of the case on 5 Jan 2009. It was reported that a female patient (62 yrs) was administered topically 0.1 ml of Duraphat for a tooth disorder (unspecified) and that she experienced (no detail on the chronology) an allergic reaction verging on an anaphylactic response (without any further detail on the reaction). The patient was hospitalized (no detail on duration) and the case was reported as life-threatening in the [redacted] On 22 January 2009, a consumer contacted Colgate to report an anaphylaxis-like reaction (but not as bad) after application of Duraphat Varnish by her dentist. The reaction occurred on the same date as the case in the report from the [redacted], the patient was the same sex and same age and had in both cases known allergies to fluorescein. The patient reported that she developed weakness, with heart racing, nervousness, trembling, incoherent speech and a swelling of the lips. After the dentist had removed the varnish, she went to the hospital. Three hours later she felt better and left the hospital. In the past (7 Nov 2008) she was also treated with Duraphat Varnish and said she had heart racing for a few seconds. The dentist was contacted on 4 Feb 2009. He confirmed having informed [redacted] about the reaction through a yellow card. However, he denied that the case was life-threatening. The patient has several concomitant medications including Hormone Replacement Therapy, Thyroxin, Circadin, Lacrilube Eye Ointment, Gaviscon Advance, Paracetamol. She has a history of allergies to Fluorescein, Lignocain, Proxymetacain, bee stings and has many food intolerances (no details). The patient also has Myalgic Encephalomyelitis.	
The case is serious due to medical significance. Due to the number of concomitant medications and known intolerances of the subject, it is difficult to link with certainty the reactions to the use of Duraphat Varnish. However, a potential relatedness is not excluded according to the chronology of events and the fact the patient already had a slight reaction on the first use of the product. The MAH assesses the causality between the reactions and the product as possible.	

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- The third case was initially reported as non-serious and upgraded as serious (medically significant) later on by the dentist, on the basis of additional symptoms reported by the patient.

• [redacted]	
Source	Dentist
Reactions	Initial report: Swelling and pain after local application. Follow-up report: Right cervico-facial adenopathy. Significant fatigue and somnolence during 24 hrs.
Short assessment	The case is serious (medically significant) according to the

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	reporter. The case is unlisted.
Short narrative:	
A dentist reported that a male patient experienced swelling and pain after a local application of Duraphat suspension for teeth. The patient had no concomitant medication and the reporter assessed the events as being possibly related to the use of Duraphat. At a follow-up visit, the patient reported new events: a right adenopathy, important fatigue and somnolence during 24 hours. The patient visited his doctor 24 hours after application of the product and was treated with Eludril, Birodogyl and Ibuprofen. The patient recovered totally after 72 hours. The dentist upgraded the case as serious (medically significant).	
Causality is classified as "possible". However, it may be considered 'doubtful' due to the following reasons: According to the type of active ingredient in Duraphat, to its mode of action, to the absence of known systemic absorption and to the clinical experience with the product, the symptoms (adenopathy, somnolence, fatigue) that have led to the upgrade into a serious ADR are considered as being unlikely or doubtfully related to the use of the product by the MAH. Furthermore, the complete and quick resolution of the events after treatment with antibiotics give us argument to consider that the events considered in this case have been rather related to another reason than the application of Duraphat Varnish.	

- The fourth case concerns a medically important reaction in a subject with known allergies to colophonium and for whom the product was contra-indicated. It occurred in [redacted] where the concentration of colophonium is twice higher than in [redacted]

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• [redacted]	
Source	Dental Office
Reactions	Swelling face, Swelling of lips, Swelling of tongue, Tingling mouth
Short assessment	The case is serious. The case is unlisted.
Short narrative:	

The case was reported by a dental office for the Dentist. PreviDent 5% Sodium Fluoride Varnish was applied to the teeth of a 49-year-old female, who has allergies to palm oil, colophony and rosin. While applying this product, the patient experienced tingling in her mouth and lip swelling. When the patient left the dental office, she was still experiencing the tingling mouth and swollen lips. One day after application, the patient reported waking up in the morning with swelling to her face, lips and tongue. She was taken to a local emergency room (length of stay unknown) that same day where an Epi Pen was administered for the allergic reaction. The patient was discharged from the emergency room (date unknown) with a prescription for oral prednisone and an unspecified medication (dosage and frequency unknown). Follow-up information confirmed that the patient was doing fine and continued to take prednisone.
Causality: The reporter confirmed that the events experienced by the patient were considered to be medically important and likely due to the product.

6.4.2 Serious Listed Reports

There were no serious listed reactions reported between July 2007 and June 2010.

6.4.3 Non-Serious Unlisted Reports

In the reporting period of this PSUR forty-one non-serious unlisted case reports have been spontaneously reported.

Overall most of these reactions were related to irritation or dryness (24 reports) in the oral cavity. There were also 5 reports related to a reaction of hypersensitivity and 7 including skin reactions. In 5 cases, patients reported nausea. Other cases include tooth discolouration, pain or accidental contact with the eyes.

Some cases were selected for the narrative:

- Some examples of irritation in the oral cavity

• [redacted]	
Source	Dentist
Reactions	Burning feeling in mouth, oesophagus, throat and teeth, nausea, mouth irritation
Short assessment	The case is non-serious. The overall case is unlisted.
Short narrative:	

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Duraphat was applied in the dental clinic on the teeth of a female patient. It was applied only once. The teeth were brushed 24 hours later to remove the product. The patient experienced a strong burning feeling in the mouth, oesophagus and throat. Six weeks later the patient still had a burning feeling in the mouth and on the teeth where Duraphat was applied. She visited a "ears-nose-throat" doctor who did not notice anything abnormal on the tissues. The person also takes other drugs (unspecified).
Causality: The dentist commented that the imputability of the reaction to Duraphat is "questionable". However, there is not enough information to totally exclude a causal relationship and therefore the causality is assessed as "Possible".

• [redacted]ce	
Source	Dentist (same as case [redacted]
Reactions	Cheilitis
Short assessment	The case is non-serious and unlisted.
Short narrative: A female patient (25-30 years) who suffered from sensitivity of the neck of the teeth was prescribed Duraphat Varnish for 1 month. The patient was advised on how to apply the product by the dentist at a frequency of one application 2 to 3 times a week after brushing teeth at night. Approximately 1 week after the start of the treatment, the patient presented with (syn)cheilitis and stopped the treatment. The patient recovered on an unknown date. The case is linked to case [redacted]	
Causality: the case may be possibly attributed to the application of the product although very few details were provided for a precise assessment.	

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• [redacted]	
Source	[redacted]
Reactions	Gingival erythema, oedema, blisters and pain; high temperature
Short assessment	The case is non-serious. The case is unlisted
Short narrative: BfarM reported this case through a letter to the MAH. A female patient (49 years) developed reddening and oedema of the gingival after an application of Duraphat. On the 2nd to 4th days after application, blisters and pain on the gingiva were noticed as well as elevated temperature. No more information was obtained.	
Causality: although there is insufficient information for a proper causality assessment, for a spontaneous report the causality is assessed as "Possible".	

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• [redacted]	
Source	Dentist

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Reactions	Application site irritation
Short assessment	The cases are non-serious. The cases are unlisted
Short narrative: A dentist from a University, who had given some young children (age between 3 and 11) some Prevident Varnish, reported that no more than 12 kids had experienced a burning sensation shortly after application of the product. The sensation was still present about five minutes later. The dentist had no information on the children and said that he would not come back into contact with the children. No more information was obtained.	
Causality: although there is insufficient information for a proper causality assessment, for a spontaneous report the causality is assessed as "Possible". The number of patients has been defined as 12 although there is no clear identification of the patients.	

• [redacted]	
Source	Dental assistant and consumer's mother
Reactions	Gingival swelling, gingivitis, gingival pain, oedema mucosal, mucosal inflammation, oral pain, lip swelling
Short assessment	The case is non-serious. The overall case is unlisted.
Short narrative: The reporter, a dental assistant and consumer's mother, reported that her daughter was treated at the dental office with Prevident 5 % Varnish for the first time, with a liberal amount of product applied on two teeth. On the morning of the following day, the consumer woke up with swollen, painful and inflamed gums and mucosal lining. After first becoming worse when waking up, the reaction leveled out. The consumer has sensitivities to many different things, including colophonium.	
Causality: The case is considered as non-serious, possibly related to the use of the product and unexpected. The product was contra-indicated in case of known sensitivity to colophonium.	

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- Reports of hypersensitivity or suspected allergic reactions

• [redacted]	
Source	Dentist
Reactions	Hypersensitivity, lip swelling
Short assessment	The case is non-serious. The case is unlisted.
Short narrative:	

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A dentist reported that a male patient visited him with lip swelling. After treatment with anti-allergic drugs, he recovered completely. Some time later (in the same month, unspecified), the patient was treated with Duraphat Varnish for gingivitis. The patient presented swelling of lips after the application. The patient recovered. On the following month, the patient reported a similar reaction after using an oral rinse. The patient has a history of allergies.
Causality: The reaction is assessed as possible (cannot be excluded) although the dentist considered the reaction was more likely due to his gloves.

• [redacted]	
Source	Physician
Reactions	Hypersensitivity, dyspnoea
Short assessment	The case is non-serious. The case is unlisted.
Short narrative: A physician reported that he had seen a patient at the hospital who had an allergic reaction with breathing difficulty to Prevident Varnish. The patient received Benadryl, Epi and Steroids and was released from the hospital. The physician requested the ingredient list and did not provide any further details.	
Causality: The reaction is assessed as possible although no details on the chronology of events or other possible causes were provided. The case is assessed non-serious as the patient was released from the hospital after the treatment and we did not get sufficient details to estimate the severity of the reaction.	

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• [redacted]	
Source	Dermatologist
Reactions	Swelling of lips, face and fingers
Short assessment	The case is non-serious. The case is unlisted.
Short narrative: A dermatologist reported that she saw a 16 year old male patient with very swollen lips after he had a treatment, on the day before, with Prevident Varnish at the dental office. The lips and the face were swollen when he woke up in the morning. His finger also was swollen after he put it in his mouth. The patient had known sensitivity to tree sap and tree nuts and the dermatologist mainly enquired to see if these ingredients could be present in the product. No more information was provided.	
Causality: The reaction is assessed as possibly related.	

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• [redacted]	
Source	Dentist

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Reactions	Allergic reaction on upper lip down to neck and partially on the chest (red blotches)
Short assessment	The case is non-serious and unlisted.
Short narrative: A dentist reported that her female patient experienced an allergic reaction with red blotches (not like hives) on the upper lip down to the neck and partially on the chest. She has been using the product sparingly for 8 months and the reaction developed when she started to use it more frequently.	
Causality is assessed as possible.	

- Examples of reports of nausea

• [redacted]	
Source	Dentist
Reactions	Nausea, vomiting, headache
Short assessment	The case is non-serious. The case is unlisted.
Short narrative: A female patient (12 years) was treated with Duraphat by her dentist. The patient felt nausea a few minutes after application and vomited 30-45 minutes later. The patient recovered. The patient used the product for the first time. A follow-up report from the patient also referred to headache after product application.	
Causality: Although the dentist commented that the symptoms may be due to a common cold, causality cannot be excluded and is assessed as possible.	

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• [redacted]	
Source	Dentist
Reactions	Nausea, abdominal pain
Short assessment	The case is non-serious. The case is unlisted.
Short narrative: A dentist reported that her hygienist used Prevident Varnish on two brothers who both experienced severe nausea. The dentist was not sure how it was used, but it was not with a mouth tray. The varnish was only used one time on the two brothers on October 3rd and the nausea and stomach pains were experienced by the two brothers later on the same day. Parents brushed the children's teeth and let them lie down for a bit and the children started to feel better. The dentist was not certain how long the nausea and stomach pain lasted.	
Causality: Causality relationship with the product cannot be excluded and is assessed as possible.	

• [redacted]	
Source	Dental hygienist
Reactions	Nausea, eructation, malaise
Short assessment	The case is non-serious. The case is unlisted.
Short narrative: A dental hygienist reported that a female patient (24 years) was treated for acid erosion along the top of teeth and for some gum disease on one corner of teeth. The dental hygienist first used Neutrafluor 9000 (toothpaste with 9000 ppm NaF) for 3-4 minutes in a disposable tray and then applied Duraphat - less than 1 cm worth – right along gum line on one side. After treatment, consumer was still in reception when she complained that she felt queasy/nauseous and "could not stop burping." The patient was re-contacted and said she had been burping for the whole day and had been unwell for the whole week-end.	
Causality: Causality relationship with the product cannot be established with certainty on the basis of the available information and is assessed as possible.	

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- Examples of skin reaction

• [redacted]	
Source	Dentist (same as case [redacted]
Reactions	Cheilitis, dermatitis
Short assessment	The case is non-serious and unlisted.
Short narrative: A male patient (25-30 years) who suffered from sensitivity of the neck of the teeth was prescribed Duraphat Varnish for 1 month. The patient was advised on how to apply the product by the dentist at a frequency of one application 2 to 3 times a week after the night brushing of the teeth. Approximately 1 week after the start of the treatment, the patient presented with (syn)cheilitis and skin irritation of the external side of the lips and stopped the treatment. The patient recovered on an unknown date. The case is linked to cas[redacted]	
Causality: the case may be possibly attributed to the application of the product although very few details were provided for a precise assessment.	

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• [redacted]	
Source	Dental hygienist
Reactions	Swelling face
Short assessment	The case is non-serious and unlisted.
Short narrative:	

A dental hygienist reported that she applied Prevident 5 % Varnish to a female patient on all teeth as indicated. The day after, the patient called the office to report that she woke up and had her face swollen. No further details were provided.
Causality: the case may be possibly attributed to the application of the product although very few details were provided for a precise assessment.

- 1 case of tooth discolouration

• [redacted]	
Source	Dentist
Reactions	Tooth discolouration
Short assessment	The case is non-serious. The case is unlisted.
Short narrative: A female patient was prescribed Duraphat by her dentist. Duraphat was applied by the patient herself twice a day for 3 days. A yellowish coating of the product was left on her teeth. The coating was removed mechanically by the dentist with a toothbrush. The patient had no concomitant medication, but she is a smoker.	
Causality is assessed as possible.	

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- 1 report of a reaction in a person for whom the product was contra-indicated

• [redacted]	
Source	Dentist
Reactions	Oedema mouth, Oral mucosal exfoliation, Gingival erythema, Gingival pain, Gingival blisters, Oropharyngeal pain, Pharyngeal erythema
Short assessment	The case is non-serious. The overall case is considered unlisted due to some reactions which are not listed in the CCSI. However, the product is contra-indicated in the SmPC for subjects with known sensitivity to the excipients (colophony) as it is in this report.
Short narrative: A dentist reported that a male patient experienced a reaction (Gingiva, throat and upper palate. reddening, swelling, aching, blisters/aphtae) a couple of hours after application of Duraphat Varnish. The reaction lasted for many days. The product was applied with a cotton pad as described in the PIL. The mouth was not rinsed out after use. The product was used before and he did not have such a reaction. The product was withdrawn at the time of the report. The patient has recovered. He did not use other products at the same time, has no other diseases in his mouth and did not smoke. However, he has known allergies to abietin acid and colophonium. According to the dentist, the reaction was not serious, but there is a certain correlation with the product according to the results of an EAV tests (Electro Dermal screening).	
Causality is assessed as certain.	

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6.4.4 Non-Serious Listed Reports

There were six non-serious listed reactions reported between July 2007 and June 2010 concerning minor local reactions. Five of them concern swelling reactions of lips or mouth and one concerned some oral discomfort. One case is described below as an example:

• [redacted]	
Source	Dentist
Reactions	Stomatitis, oedema mouth
Short assessment	The case is non-serious. The case is listed.
Short narrative: A dentist reported that a female patient who had been treated with Duraphat Varnish developed irritation and swelling of the oral mucosa. However, the dentist was unsure that the reaction was due to Duraphat. There was no indication on the outcome of the reaction.	
Causality: The reaction is assessed as possible although the dentist is unsure it is due to the product.	

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6.5 All Death Cases

No fatal cases were reported within the period under review.

7. STUDIES

7.1 Newly analyzed Company-Sponsored Studies

There were no new sponsored studies carried out within the period of this report.

7.2 Targeted New Safety Studies

There is no safety study planned on Duraphat. However, one efficacy study is running in France to evaluate the impact of applying a fluoride varnish on the prevention of carries in elderly persons hospitalized for long term in healthcare institutes. The duration of the study is 2 years; the study population is 300 subjects, with an estimate natural death rate of 40 % in the test population. Adverse events/reactions during the study will be collected and analyzed. No adverse reactions were reported at the time of this report.

7.3 Published Safety Studies

Colgate-Palmolive has carried out searches for any independent published studies cited in medical and scientific journals where the product or its ingredient may have been used in

safety studies/clinical trials. Two publications providing relevant safety information to the safety of Duraphat Varnish or its main active ingredient, sodium fluoride, have been considered, as well as two recently published efficacy studies reinforcing the benefit of using Duraphat varnish in two different populations.

References and summaries for these published studies are provided in Appendix 7 .

Two of those studies referred to animal studies showing an effect of sodium fluoride ingestion on male mouse/rats fertility (ref 1 and 2). One referred to an animal study showing a neurofunctional effect of sodium fluoride, administered by intragastric gavage, during the developmental stage of male rats (ref 3). One showed that intoxication of rats for 30 days with high doses of sodium fluoride has potentially deleterious effects on learning and memory (ref 4).

One study on seven children (ref 5) shows a transitory increase in the urinary fluoride after topical application of Duraphat in a population of seven 5-year-old children, with a return to normal level within 48 hours.

The two last studies (ref 6 and 7) refer to efficacy studies and confirm the benefit of using Duraphat Varnish in controlling root caries development in the elderly population and as a desensitizing agent in a population with hypersensitive teeth.

7.4 Other Studies

There have been no specific studies carried out on pregnant patients and no relevant safety information was reported related to pregnancy exposure during the period of this report.

8. OTHER INFORMATION

Since the data-lock point (30 June 2010) no relevant new information that might affect the interpretation or evaluation of existing reports has come to our knowledge.

During the period of this PSUR, 3 case reports were collected from the [redacted] Ministry of Health website which concern reactions to Sodium Fluoride. However, it is unclear from which type of product, from which type of administration and for which dose these reactions occurred. Briefly, they are:

- A female patient (initials [redacted]) developed an allergic reaction on May 28, 2010 with sodium fluoride. The case was non-serious and the patient recovered (report reference on the website: [redacted]
- A male child patient (initials [redacted]) developed abdominal pain, cold sweat and vomiting after accidental ingestion of sodium fluoride on October 13, 2008. The case was non-serious. (report reference on the website: [redacted]
- A male patient (initials [redacted]) developed mucosal swelling and pharyngeal erythema after use of sodium fluoride on January 27, 2008. The case was non-serious and the patient condition improved afterwards (report reference on the website: [redacted]

B

B

One allergic reactions considered as serious was also reported under the form of Anonymized Single Patient Report (ASPR) by the [redacted] but concerned another products containing sodium fluoride (a mouthwash) from which other constituent than fluoride could have caused the reactions (ASPR reference: [redacted] dated 16 March 2010).

B

8.1. Lack of efficacy

One case of lack of efficacy was referred to us, over the period of this report, by a patient who complained that the product did not want to dry on the teeth after the application and became stringy (internal reference [redacted] No further details were provided by the patient.

B

8.2. Late breaking information.

Since the data-lock point, there has been no new late breaking information brought to our attention.

8.3 Risk Management Plan

No Risk management Plan is in place for this product.

8.4 Risk-Benefit Analysis Report

As no relevant change in the risk of the product has been identified, no specific risk-benefit analysis has been conducted on this product.

9. OVERALL SAFETY EVALUATION

None of the individual reports received provides sufficient evidence to confirm an obvious causal relationship with Duraphat, except for three cases for which the product was contra-indicated (known allergy to one of the excipients).

Confounding factors obscuring the case should also be considered which may include concomitant medications, underlying diseases (i.e. caries) and stress from dental visits and teeth treatments. In addition, most of the cases were reported by dentists which may indicate that patients could already have pre-existing dental disorders. Furthermore, some dentists have questioned the causal relationship of the reaction with the use of the product. Those cases were, however, reported as the causal relationship could not be totally excluded

The four cases classified as serious during the period of the PSUR do not provide clear evidence of a causal relationship with the use of Duraphat or occurred in patients for who the product was contra-indicated due to a known sensitivity to one of the ingredients. In one case, the reporting dentist questioned the seriousness of the case and its relatedness with the use of Duraphat. Similarly, in a second case, the dentist assessed the causality as doubtful but, could not exclude a relationship with the product. The number of concomitant medications and the history of potential allergic reactions for a third subject

make it difficult for the company to relate the reaction to the use of Duraphat with certainty. However, the chronology of the events and the slight reaction to the product during a prior use make the causal relationship possible.

9.1 Cumulative Perspective: Serious Unlisted Reactions

Throughout the reporting period, there were 4 serious unlisted reports for a total of more than [redacted] doses of Duraphat Varnish/suspension or more than [redacted] patient years.

A

Previously, and since 1997 when Colgate acquired the product, no other serious unlisted adverse drug reactions had been observed. Furthermore, the 4 cases reported in this PSUR were not related with sufficient evidence to the use of the product and are very different in their nature from each other. As such, at the time of this PSUR reporting period, there was no significant basis identified to change the safety profile of the product.

9.2 Cumulative perspective: Non-Serious Unlisted Reactions

There were forty-one non-serious unlisted reactions reported by healthcare professionals during the reporting period leading to 71 unlisted preferred MedDRA terms overall. However, there is no evidence of a significant increased frequency over time of a specific type of reaction.

9.3 Increased Reporting Frequency of Listed Reactions

Since there were only six listed reactions observed throughout the reporting period. There is no evidence of a relevant increased frequency over time of a specific type of reaction.

9.4 Changes in Characteristics of Listed Reactions

Since there is no sufficient evidence to confirm the causal relationship with Duraphat Varnish for most of the unlisted reactions observed throughout the reporting period, there is no recommendation for a change in the characteristics of listed/expected reactions.

9.5 Interactions

Some reactions were reported after the patients had used 2 products successively on the teeth (Neutrafluor 9000 in case [redacted] Durashield Varnish in cases [redacted] and [redacted] dental floss in case [redacted]). However, the observed reactions may be due to one of the two products in each case and there is no evidence of an interaction of Duraphat with other ingredients or drugs from the analysis of the cases presented in this report.

B

9.6 Experience with overdose

There were no reports of overdose during the period of this report.

9.7 Abuse and misuse

There were no reports of abuse during the period of this report.

One case of misuse was reported which does not bring any relevant new safety information about the product. The case is summarized here below. It has not been incorporated into the line listing.

• [redacted]	
Source	Dentist
Reactions	Sticking to the teeth
Short assessment	The case is non-serious. The case is unexpected.
Short narrative: A dentist prescribed Duraphat Varnish to a patient by mistake instead of Duraphat toothpaste. Upon application, the male patient noticed that Duraphat Varnish was sticking to the teeth and to the toothbrush and informed the dentist. After scratching the product from the teeth, the patient recovered.	
Causality is assessed as certain, by misuse.	

B

Four cases were reported in subjects with known sensitivity to colophonium, while the product was contra-indicated in such patients.

9.8 Experience with pregnancy and lactation

There were no reports of drug reaction involving pregnant or breast-feeding patients during the period of this report.

9.9 Experience in special patient groups

The distribution of ADRs was as follows:

Category	Related age	Number of ADRs
Newborn infants	0-27 days	0
Infants	28 days – 23 months	0
Children	2 – 11 years	16*
Adolescent	12 – 16 years	3
Adults	17 – 64 years	18
Seniors	65 years and more	1
Not indicated		13

* including 12 cases reported simultaneously from a same dentist.

Gender	Number
Male	11
Female	25
Not indicated	15

In several reports, the gender or the age of the patient was not disclosed.

For the cases for which the age is known, 16 case reports involved children. However, such a high proportion is mainly due to the reporting of 12 cases involving children by a same dentist. Otherwise, most of the other cases were reported from adult patients.

In two thirds of the reports the sex of the subject was obtained with a majority of female patients as it is usually found from spontaneous reports..

Overall, reactions involving these patient groups did not provide any specific signals for a specific population versus the others.

9.10 Effects of long-term treatments

There were no reports of long-term treatment with Duraphat during the period of this report.

9.11 Cases from non-health care professionals

Five spontaneous reports from consumers were received during the period of this report. They are summarized in Appendix 5 and they do not bring any new relevant information for the assessment of the risk-benefit of Duraphat Varnish.

9.12 Prescription errors/medication errors

One prescription mistake was reported and led to a misuse of the product. The case is described under section 9.7 Misuse. The case is isolated and does not require any change in the instructions for use in the Product Information Leaflet.

10. CONCLUSIONS

The experience gained during the period covered by this report confirms the established safety profile of Duraphat.

Overall, the proposed Summary of Product Characteristics, modified to harmonize with the CCSI, contains sufficient information to inform physicians and patients about the occurrence of adverse drug reactions and to warrant the safe use of Duraphat which still has an excellent risk-benefit ratio when used under the conditions stipulated in the Summary of Product Characteristics.

APPENDIX 1

CORE COMPANY SAFETY INFORMATION

NAME OF THE MEDICINAL PRODUCT

UK, PT, IT	Duraphat 50 mg/ml Dental Suspension
FR	Duraphat 50 mg/ml Dental Suspension
GE	Duraphat
DK	Duraphat
FN	Duraphat® 22.6 mg F-/ml dental suspension
Ice	Duraphat
NO	Duraphat
SE	Duraphat 22.6 mg/ml dental suspension
CH	DURAPHAT®, Suspension Fluoridierungslack
NL	DURAPHAT®
GR	Duraphat 50 mg/ml Dental Suspension
PL	Duraphat, 50 mg/ml, dental suspension

Posology and Method of Administration (Ref 4.2 of CCDS)

Duraphat 50 mg/ml Dental Suspension is to be applied by the dentist. Before applying Duraphat, excess plaque should be removed and the teeth dried. Duraphat is applied as a thin layer to the most susceptible areas of dentition using a brush, probe or swab.

Recommended dosage for single application:
For milk teeth: up to 0.25 -0.3 ml (=5.65-5.7 mg Fluoride)
For mixed dentition: up to 0.40 ml (=9.0-9.04 mg Fluoride)
For permanent dentition: up to 0.75 – 1.0 ml (=16.95-17 mg Fluoride)
For caries prophylaxis, the application is usually repeated every 6 months but more frequent applications (every 3 months) may be made.
For hypersensitivity, 2 or 3 applications should be made within a few days.
The patient should not brush the teeth or chew food for 4 hours after treatment.

Method of administration: For dental use.

Contraindications (Ref 4.3 of CCDS)

Hypersensitivity to any constituent
Ulcerative gingivitis
Stomatitis
Bronchial asthma

Special Warnings and Precautions for Use (Ref 4.4 of CCDS)

Application of Duraphat 50 mg/ml Dental Suspension to the whole dentition should not be carried out on an empty stomach.
On the day when Duraphat has been applied, high doses of fluoride preparations, such as fluoride gels, should not be used. The administration of Fluoride supplements should be suspended for several days after applying Duraphat.

Interaction with other Medicinal Products and other forms of Interaction (Ref 4.5 of CCDS)

The presence of alcohol in the Duraphat formula should be considered.

Pregnancy and Lactation (Ref 4.6 of CCDS)

As this product contains 33.8% of ethanol (each dose contains up to 0.2 g of alcohol), it is recommended to avoid its use in pregnant women and during lactation.

Effects on Ability to Drive and Use Machines (Ref 4.7 of CCDS)

None known.

Undesirable Effects (Ref 4.8 of CCDS)

Gastrointestinal disorders:
Stomatitis, gingivitis ulcerative, retching and oedema mouth
Skin and subcutaneous tissue disorders:
Skin irritation, angioedema
Respiratory, thoracic and mediastinal disorders:
Asthma

Overdose (Ref 4.9 of CCDS)

In very high doses, fluoride has an acute toxic effect. Doses of several milligrams of fluoride per kg of body weight may cause nausea, vomiting, and diarrhoea. Later on, tetany and convulsions can occur, as well as cardiovascular disorders.

Pharmacodynamic Properties (Ref 5.1 of CCDS)

Pharmaco-therapeutic group: caries prophylactic agents

The anti-caries properties of Duraphat are due to the effect of fluoride applied topically after tooth eruption reduce caries by inhibiting demineralisation and promoting re-mineralization of the tooth surface and by inhibiting the cariogenic microbial process.

Duraphat dental suspension also reduces dentinal hypersensitivity.

In the treatment of dental erosion associated with frequent consumption of acidic beverages or gastric reflux, high concentration topical fluoride agents, such as Duraphat, are considered to be of value.

Pharmacokinetic Properties (Ref 5.2 of CCDS)

After oral administration, fluoride absorption is rapid and extensive (90-100%) with peak fluoride plasma levels reached within 30 to 60 minutes after ingestion. Fluoride is widely distributed through the body and concentrates in bone and teeth. About 50% of fluoride is stored. Excretion is primarily through the kidneys with less than 10% being excreted in the faeces and less than 1% in sweat and saliva.

However, when fluoride is administered locally, systemic absorption is minimal. Duraphat covers teeth with a film of suspension which hardens in the presence of saliva. It then persists and over the following hours, causes fluoride to accumulate at a measurable depth in the tooth enamel.

Preclinical Safety Data (Ref 5.3 of CCDS)

The product is used under total control of the dentist and the amount of fluoride introduced to the patient at one time is within acceptable safety limits. The recommended doses are up to 1.0 ml for permanent dentition. Treatment is recommended every 6 months or a maximum of every three months. For hypersensitivity, 2-3 applications are recommended within a few days. These levels of fluoride introduced are again within acceptable safety limits.

Incompatibilities (Ref 6.2 of the CCDS)

None known

Revision date:

February 2010

APPENDIX 2 :

SUMMARY OF PRODUCT CHARACTERISTICS (English translation)

1. Name of the medicinal product

Duraphat 50 mg/ml, dental suspension

2. Qualitative and Quantitative Composition

1 ml suspension contains 50 mg sodium fluoride (5% m/v) corresponding to 22.6 mg fluoride (2.26% m/v), suspended in an alcoholic solution of natural waxes.
For a full list of excipients, see section 6.1

3. Pharmaceutical Form

Dental suspension

4. Clinical Particulars

4.1 Therapeutic Indications

For the prevention of caries in children and adults as part of a comprehensive control program.

For the:
prevention of recurring (or marginal) caries
prevention of progression of caries
prevention of decalcification around orthodontic appliances
prevention of caries in pits and fissures (occlusal caries)

For the desensitisation of hypersensitive elements as part of a treatment regimen which includes the daily use of suitable toothpaste.

4.2 Posology and Method of Administration

Duraphat suspension is to be applied by a dentist. Before applying Duraphat, excess plaque should be removed and the teeth dried. Duraphat is applied as a thin layer to the most susceptible areas of dentition using a brush, probe or swab.

Recommended dosage for a single administration:
For milk teeth: up to 0.25 ml (= 5.65 mg fluoride)
For mixed dentition: up to 0.40 ml (= 9.04 mg fluoride)
For permanent dentition: up to 0.75 ml (= 16.95 mg fluoride)

For caries prophylaxis, the application is usually repeated every 6 months, but more frequent applications (every 3 months) may be made.
For hypersensitivity, 2-3 applications are recommended within a few days.
The patient should not brush the teeth or chew food for 4 hours after treatment.

Method of administration
If necessary the teeth should be brushed, especially at the sites most susceptible to caries. When a group of patients is treated (for example children), the patients need to clean their own teeth using a toothbrush.

To start, clear one or two quadrants of excess saliva using an air syringe (or dabbing with cellulose). With a small cotton swab, probe or brush, Duraphat is applied directly from the tube, painting and dabbing repeatedly to form a thin layer. Then treat the next quadrants in the same manner. It is advised to first apply the suspension to the teeth in the lower jaw before too much saliva collects there, making application more difficult. It may not be necessary to paint the lingual surfaces since these are usually more caries-resistant. Duraphat should preferably be applied to those places most susceptible to caries attack.

Application of Duraphat from the cylinder is particularly suited to targeted, low-dose application. A blunt cannula is used with the end bent to an angle to facilitate application to approximal and distal surfaces. For application to approximal surfaces place the cannula between adjacent teeth and deliver a small amount of Duraphat. The dental suspension should be applied from both sides of the interproximal space and occlusally.

For fissures, a drop of Duraphat should be spread along the fissure using the cannula. Edges of fillings and crowns and hypersensitive tooth necks can be treated in the same way.

The smooth surfaces of the element should be treated when caries activity is high, particularly if decalcification is evident. The cannula should be placed tangentially to the teeth, after which some Duraphat should be distributed with the side of the curved cannula end.

Areas around fixed orthodontic aids can be treated with Duraphat by using the cannula.

The yellowish colour of Duraphat facilitates its application and control. Duraphat sets in the presence of saliva. The effect of Duraphat depends on the prolonged activity of the fluoride. The lacquer film should not be removed prematurely. Patients should be advised not to brush their teeth or chew food for at least 4 hours after treatment; during this time, soft foods and liquids may be consumed. However, if needed, the lacquer layer can easily be removed by brushing or rinsing.

Instruments, clothing etc. which come into contact with Duraphat can be cleaned with alcohol.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients
Hypersensitivity to colophony
Ulcerating gingivitis
Stomatitis
Bronchial asthma

4.4. Special Warnings and Special Precautions for Use

Application of Duraphat to whole dentition should not be carried out on patients with an empty stomach.
On the day of Duraphat application no high-dose fluoride preparations, such as fluoride gels, should be used. The administration of fluoride supplements should be suspended for several days after applying Duraphat.

4.5. Interactions with other medicinal products and other forms of interaction

The presence of alcohol in the Duraphat composition must be considered.

4.6. Pregnancy and Lactation

As this product contains 33.8% of ethanol (each does contains up to 0.2 g of alcohol), it is recommended to avoid its use in pregnant women and during lactation.

4.7. Effects on Ability to Drive and Use Machines

Duraphat has no influence on the ability to drive or use machines

4.8. Undesirable Effects

In subjects with a tendency to allergic reactions, oedematous swelling of the oral mucosa has been observed in exceptional cases, especially after extensive application. If necessary, the suspension can easily be removed from the mouth by brushing and rinsing.
Ulcerating gingivitis and stomatitis have been reported by sensitive individuals. In rare cases, asthma attacks may occur in patients who have bronchial asthma.
In patients with gastric sensitivity, retching may exceptionally occur after a high dosage and extensive application.
In very rare cases, angioedema and irritation of skin may occur.

4.9 Overdose

In very high doses, fluoride has an acute toxic action through inhibition of enzymes resulting in hypocalcaemia. Doses of several milligrams of fluoride per kg body weight cause nausea, vomiting, and diarrhoe.
Later on, tetany and convulsions can occur, as well as cardiovascular disorders.
The suspension can easily be removed from the mouth by brushing and rinsing.

5. Pharmacological Properties

5.1. Pharmacodynamic Properties

Pharmacotherapeutic category: caries prophylactic agents, ATC code: A01AA01

Sodium fluoride applied topically after tooth eruption reduces caries by inhibiting demineralization and promoting remineralization of the tooth surface and inhibiting the cariogenic microbial process.

Duraphat also reduces dentinal hypersensitivity.

In the management of dental erosion associated with the frequent consumption of acidic beverages or gastro-oesophageal reflux, high concentration topical fluoride agents are considered to be of value. Duraphat is at least as effective as 2 % sodium fluoride solution in inhibiting erosion in vitro.

5.2. Pharmacokinetic Properties

After oral application, fluoride absorption is rapid and extensive (90-100%) with peak fluoride plasma levels reached within 30 to 60 minutes after ingestion. Fluoride is widely distributed through the body and concentrates in bone and teeth. About 50% of fluoride is stored. Excretion is primarily through the kidneys. Less than 10% is excreted in the faeces and less than 1% in sweat and saliva.

However, when fluoride is administered locally, systemic absorption is minimal. Duraphat covers the teeth with a film of suspension which hardens in the presence of saliva and then persists, and which over the following hours causes fluoride to accumulate at a measurable depth in the tooth enamel.

5.3. Preclinical Safety Data

This product is applied by a dentist, and the amount of fluoride introduced to the patient at one time is within acceptable safety limits. The recommended dose is up to 0.75 ml for permanent dentition. Treatment is recommended every six months or a maximum of every three months. For hypersensitivity,

2 or 3 applications are recommended within a few days. These levels of fluoride introduced are again within acceptable safety limits.

(DELETED : Due to the slow release of fluoride, the plasma levels are even lower than levels known to produce no side effects in children.)

REPLACED WITH: Due to slow release of fluoride from Duraphat Varnish, the exposure level would be well below the level that could cause toxic signs and symptoms in children.

6. Pharmaceutical Particulars

6.1. List of Excipients

Ethanol 96%
White Wax (E901)
Shellac (E904)
Colophony
Mastic
Saccharine (E954)
Raspberry essence

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

Unopened 3 years. For the aluminium tube: After opening, use within 3 months.

6.4. Special Precautions for Storage

Do not store above 25° C.

6.5 Nature and Contents of Container

Boxes with 1 x 10 ml tube or 5 x 30 ml tubes. The tubes are made of internally lacquer-coated aluminium and are externally printed. The tubes have a white plastic screw cap with sealing plug.

Boxes with 1 or 5 x 1.6 ml glass cylinders with a cream bromobutyl rubber stopper and a gold aluminium cap at the top and a dark blue chlorobutyl rubber stopper at the bottom.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special precautions required

7. Marketing Authorisation Holder

Colgate-Palmolive (UK) Ltd
Guildford Business Park
Middleton Road, Guildford, Surrey GU2 5LZ
United Kingdom

8. Marketing Authorisation Number

RVG 10942

9. Date of First Authorisation/Renewal of the Authorisation

Date of first authorization: 16 May 1990
Date of new renewal of the authorization: 03 December 2002

10. Date of Revision of the Text
Last partial revision: sections 1, 4.6, 4.8, 4.9, 6.2 and 6.6 19 January 2010

APPENDIX 3
SALES DATA, VOLUME OF UNITS SOLD (July 2007 – June 2010 Incl.)

COUNTRY	PACK SIZE	Jul-Dec 2007*	2008	2009	Jan-Jun 2010	Total
[redacted] UK	10ml tubes	[redacted]				
	5 x 1.6ml ampoules					
	5 x 30ml tubes					
France	10ml tubes					
	5 x 1.6ml ampoules					
	5 x 30ml tubes					
Italy	10ml tubes					
	5 x 1.6ml ampoules					
	5 x 30ml tubes					
Portugal	10ml tubes					
	5 x 1.6ml ampoules					
	5 x 30ml tubes					
Greece	10ml tubes					
	5 x 1.6ml ampoules					
	5 x 30ml tubes					
The Netherlands	10ml tubes					
	5 x 1.6ml ampoules					
	5 x 30ml tubes					
Europe	10ml tubes					
	5 x 1.6ml ampoules					
	5 x 30ml tubes					
Rest of World (incl Prevident Varnish)	10ml tubes	[redacted]				
	5 x 1.6ml ampoules	0				
	5 x 30ml tubes	0	0	0	0	0

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GLOBAL	10ml tubes	[redacted]									
	5 x 1.6ml ampoules	[redacted]									
	5 x 30ml tubes	[redacted]									

A

* estimated as 1/2 of full year 2007

Using this data,

[redacted]

A

Thus an estimate of total patient exposure is available

Pack Size	Total Units	Total Unit Doses
10ml tubes	[redacted]	[redacted]
5 x 1.6ml ampoules	[redacted]	[redacted]
5 x 30ml tubes	[redacted]	[redacted]
Total number of unit doses		[redacted]
Total number of patient years		[redacted]

Summary

Over the period July 2007 to June 2010 incl., there has been an estimated [redacted] doses of Duraphat (or Prevident Varnish) administered
In order to calculate patient years it has been assumed that a dose of 0.75ml is given once every day of the year.
Therefore the patient years is estimated to be: [redacted]

A

APPENDIX 4
PRESENTATION OF INDIVIDUAL CASE HISTORIES: MEDICALLY CONFIRMED REPORTS (July 2007 - June 2010)

ADR Centre No.	Date/ Year of onset	Country	Source	Age	Sex	Dosage	Treatment duration	Reaction description	SOC	PT	Outcome	Comments
1. Direct reports to MAH: all serious ADRs (n = 4)												
[redacted]	10 Dec 2008 (Rec[d] on 5 Jan 2009)	[redacted]	Authorities – report	62	F	0.1 ml	1 x	Allergic reaction verging on anaphylactic response	Immune System Disorder	Hypersensitivity	NA	Although we could not get a 100 % confirmation the 2 reports were for the same case, the MAH considered that there are sufficient evidences to link the two reports together. Unlisted
[redacted]	10 Dec 2008 (Recd on 22 and 28 Jan 2009)	[redacted]	Consumer	62	F	NA	1 x	Reported that she had a reaction like anaphylaxis[1], but not so bad, with feeling weak[3], heart racing[2], nervousness[4] and shaking[6], with incoherent speech[4] and lip swelling[5].	-Immune System Disorders[1] -Cardiac Disorders[2] -General Disorders and Administration Site Conditions[3] -Psychiatric Disorders[4] -Gastrointestinal Disorders[5] -Nervous System Disorders[6]	Anaphylactoid reaction[1] Palpitations[2] Asthenia[3] Nervousness[4] Lip swelling[5] Incoherent[6] Tremor[6]	Went to hospital, but after 3 hours, she had recovered and was released.	

B

[redacted]	Mar 2009	[redacted]	Initial: [redacted] Follow-up: dentist	26	M	Contact with a cotton pad	1 application	Dizziness 1 week long	Nervous system disorders	Dizziness	Resolved	The case was reported as serious by [redacted] but considered as non-serious by the dentist and with a questionable causality. MAH maintains [redacted] classification of serious (medically important) and possibly related. Unlisted
[redacted]	22nd Oct 2007	[redacted]	Dentist	40	M	Not reported	1 day	Swelling[1] and pain[2] after local application. Right cervico[3]-facial[4] adenopathy Significant fatigue[5] and somnolence[6] during 24 hrs.	[1,2,5]General disorders and administration siteconditions. [3]Blood and lymphatic system disorders. [4]Skin and subcutaneous tissue disorders [6]Nervous system disorders	Application site swelling[1]. Application site pain[2]. Lymphadenopathy cervical[3]. Swelling face[4]. Fatigue[5] Somnolence[6]	Resolved	The case was upgraded as serious (medically significant) by the reporter at a follow-up visit. The imputability is assessed as 'doubtful' Unlisted
[redacted]	16 Mar 2010	[redacted]	Dental office	49	F	NI	NI	Tingling in the mouth, lip swelling 1 day later, lip, tongue and face swelling	Gastrointestinal disorders Skin and subcutaneous tissue disorders	Paraesthesia oral Lip swelling Swollen tongue Swelling face	Recovered after treatment	The case is unlisted although the patient has known sensitivity to colophony which is a contra-indication for the use of the product.

B

2. Direct reports to MAH : all non-serious ADRs												
Gastrointestinal disorders (n = 23)												
[redacted]	Feb 2009	[redacted]	Dentist	57	F	NI	1 application	Burning sensation localized in mouth	Gastrointestinal disorders	Oral discomfort	NI	Unlisted
[redacted]	May 2008	[redacted]	Dentist	44	F	As recommended	3 days – 1x / day	Yellowish coating on the teeth	Gastrointestinal disorders	Tooth discolouration	Recovered	Patient is smoker – Unlisted
[redacted]	4 Sep 2008	[redacted]	Doctor	Ad.	F	NI	NI	Gums peeling , red and hurting	Gastrointestinal disorders	Oral mucosal exfoliation Gingival erythema, gingival pain	NI	Unlisted
[redacted]	Nov 2008	[redacted]	Dentist	NA	F	NA	1 X	Burning feeling of mouth, oesophagus, and teeth, nausea, mouth irritation Burning feeling of throat	Gastro-intestinal disorders Respiratory, thoracic and mediastinal disorders	Oesophageal pain, Oral discomfort, Stomatitis, Nausea, Sensitivity of teeth, Throat irritation	Still burning 6 weeks after the application	Reporter considered imputability as questionable Unlisted

B

[redacted]	Nov 2008	[redacted]	Dentist	12	F	NA	1 x	Nausea, vomiting, headache	1: Gastro-intestinal disorders 2: Nervous system disorders	Nausea Vomiting Headache	Recovered	Unlisted
[redacted]	5 Nov 2008	[redacted]	Dermato logist	16	M	Brushed on teeth	1 use	swollen lips. face and fingers	Gastro-intestinal disorders Skin and subcutaneous tissue disorders General disorders and application site conditions	Lip swelling Swelling face Oedema peripheral	Improving on next contact	He is allergic to tree nuts and tree sap? Unlisted
[redacted]	Dec 2008	[redacted]	Dentist	NA	M	NA	1 x	Swelling and desquamation of oral mucosa Gingiva, throat and upper palatine. reddening, swelling, aching, blisters	Gastro-intestinal disorders Respiratory, thoracic and mediastinal disorders	Oedema mouth Oral mucosal exfoliation Gingival erythema Gingival pain, Gingival blisters, Oropharyngeal pain, Pharyngeal erythema	Unknown	Subject has known allergy to colophonium. The product is contra-indicated to subject with known sensitivity to the excipients. Unlisted

B

[redacted]	Feb 2009	[redacted]	Dentist	50	M	As recommended	1 x	Lip swelling, allergic reaction	Gastro-intestinal disorders Immune system disorders	Lip swelling Hypersensitivity	Recovered	According to dentist, reaction is likely due to his gloves and not to the product – Unlisted
[redacted]	May 2009	[redacted]	Dentist (same as [redacted]	25-30	F	2-3 x / week	1 week	(Syn)cheilitis	Gastrointestinal disorders	Cheilitis	resolved	Unlisted
[redacted]	May 2009	[redacted]	Dentist [redacted]	25-30	M	2-3 x / week	1 week	(Syn)cheilitis and skin irritation of the external side of the lip	Gastrointestinal disorders Skin and subcutaneous tissue disorders	Cheilitis Dermatitis	resolved	Unlisted
[redacted]	28 Sep 2009	[redacted]	Dental hygienist	24	F	Less than 1 cm	1 use	Feels queasy/nauseous, burping, unwell for a week	Gastro-intestinal disorders General disorders and application site conditions	Nausea Eructation Malaise	resolved	Concomitant use of Neutrafluor 9000 to treat dental erosion Unlisted
[redacted]	26 Oct 2009	[redacted]	Dentist	child	M	NI	1 use	Severe nausea, stomach pains	Gastro-intestinal disorders	Nausea, Abdominal pain upper	Was better after cleaning the teeth	Brother of [redacted] Used first a product called Durashield Varnish Unlisted
[redacted]	26 Oct 2009	[redacted]	Dentist	child	M	NI	1 use	Severe nausea, stomach pains	Gastro-intestinal disorders	Nausea, Abdominal pain upper	Was better after cleaning the teeth	Brother of [redacted] Used first a product called Durashield Varnish Unlisted
[redacted]	Dec 2009	[redacted]	[redacted]	NI	NI	NI	NI	Gingival reddening and oedema, blisters, pain and high temperature 2-4 days later	Gastrointestinal disorders	Gingival erythema Gingival oedema, Gingival blisters	NI	Unlisted

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									General disorders and administration site conditions	Gingival pain Pyrexia		
[redacted]	08 Jun 2010	[redacted]	Dental assistant	Adult	F	Liberal amount on teeth 24 and 25	One use	Gums and mucosal lining of mouth: swollen, inflamed and painful Lower lip swollen.	Gastrointestinal disorders	Gingival oedema Oedema mucosal Gingivitis Mucosal inflammation Gingival pain Oral pain Lip swelling	Lips still swollen 1 day after treatment	Unlisted Consumer with several known allergies
[redacted]	16 Mar 2010	[redacted]	[redacted]	50	F	NI	NI	Redness and oedema of the gingival Sweating Fever	Gastrointestinal disorders Skin and subcutaneous tissue disorders General disorders and administration site conditions	Gingival erythema Gingival oedema Hyperhidrosis Pyrexia	NI	Unlisted
[redacted]	20 Jan 2010	[redacted]	Dental hygienist	11	M	0.4 ml, rinsing	NI	Mouth burning with raspberry varnish	Gastrointestinal disorders	Oral discomfort	Lasted for 1 hour	Unlisted
[redacted]	27 Jul 2009	[redacted]	Dental office	NI	F	Applied in office	Post-treatment	swelling of the lips.	Gastro-intestinal disorders	Lip swelling	NI	Patient allergic to fish and nuts Listed

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[redacted]	June 2008	[redacted]	Dentist	NA	F	NA	NA	Irritation and swelling of oral mucosa	Gastro-intestinal disorders	Stomatitis Oedema mouth	Unknown	Dentist reported to be unsure it is due to Duraphat – Listed
[redacted]	29 Aug 2008	[redacted]	Dental surgeon	child	F	NI	NI	Lips swelled up.	Gastro-intestinal disorders	Lip swelling	NI	Happened 11 years ago. No more details. Listed
[redacted]	25 Jan 2010	[redacted]	dentist	Sr – over 70	F	Applied to 4 teeth	NI	Lips swelling	Gastrointestinal disorders	Lip swelling	NI	Same dentist as [redacted] Listed
[redacted]	04 Feb 2010	[redacted]	Dentist	NI	NI	NI	NI	Lower lip swelling	Gastrointestinal disorders	Lip swelling	NI	Listed
[redacted]	05 Feb 2010	[redacted]	Dentist	Adult	F	NI	First time use	Upper lip swelling	Gastrointestinal disorders	Lip swelling	NI	Listed
Immune system disorders (n = 3)												
[redacted]	1 Nov 2007	[redacted]	dentist	NA	F	NA	Sparingly for 8 months and weekly for last 2 weeks	Allergic reaction on upper lip down to neck (red blotches)	1st: Immune system disorders 2nd: Skin and subcutaneous tissue disorders	Hypersensitivity Rash Macular	Unknown	Unlisted

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[redacted]	2 Mar 2009	[redacted]	Physician	NI	F	NI	NI	Allergic reaction, breathing difficulties	Immune system disorders Respiratory, thoracic and mediastinal disorders	Hypersensitivity Dyspnoea	Resolved after treatment with Benadryl, Epipen and Steroid	Unlisted
[redacted]	19 Mar 2009	[redacted]	Dental office	NI	F	NI	NI	Allergic reaction	Immune system disorders	Hypersensitivity	NI	Patient allergic to berries Unlisted
General disorders and application site conditions (n = 14)												
[redacted]	2 Jan 2008	[redacted]	Dentist	Children : 3-11 yrs	NI	Normal use	1 use	No more than a dozen kids experienced a burning sensation after use.	General disorders and application site conditions	Application site irritation	Not recovered after 5 min	Number of patients unclear; very few information Unlisted
[redacted]	19 Mar 2009	[redacted]	Dental hygienist	NI	NI	NI	NI	Reaction	General disorders and application site conditions	Application site reaction	NI	Patient allergic to berries Unlisted
[redacted]	22 Jun 2010	[redacted]	Pharmacist	Adult	F	NI	NI	Pain in body	General disorders and application site conditions	Pain	NI	Unlisted
Skin and subcutaneous tissue disorders (n = 6)												

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[redacted]	14 Nov 2008	[redacted]	Dental office	Ad.	F	NI	Used yesterday.	Pimply like areas on the outside of lips	Skin and subcutaneous tissue disorders	Acne	NI	Reporter unsure if related to product. Unlisted
[redacted]	8 Dec 2008	[redacted]	Dental assistant	NI	M	NI	Applied 3 days ago	Applied 3 days ago and now each time he is using dental floss he gets hives, possibly an allergic reaction	Skin and subcutaneous tissue disorders Immune system disorders	Urticaria Hypersensitivity	NI	Can also be caused by the dental floss. Unlisted
[redacted]	30 Nov 2009	[redacted]	Dentist	13	M	NI	NI	Rash all over the body	Skin and subcutaneous tissue disorders	Rash	Resolved after Benadryl treatment	Unlisted
[redacted]	25 Jan 2010	[redacted]	Dentist	30's	F	NI	NI	Face swelling	Skin and subcutaneous tissue disorders	Swelling face	NI	Same dentist as [redacted] Unlisted
[redacted]	5 Mar 2010	[redacted]	Dentist	Adult	F	NI	One use	Swollen cheek	Skin and subcutaneous tissue disorders	Swelling face	Recovered	Unlisted Known sensitivity to colophony
[redacted]	15 Jun 2010	[redacted]	Dental office	Adult	F	Applied to all teeth as indicated	NI	Face swelling	Skin and subcutaneous tissue disorders	Swelling face	NI	Unlisted
Injury, poisoning and procedural complications (n = 1)												
[redacted]	6 Feb 2008	[redacted]	Dental office	NI	F	Not relevant	Not relevant	Rubbed product in eye, eye burning sensation.	Injury, poisoning and procedural complications Eye disorders	Accidental exposure Eye irritation	NI	Unlisted

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APPENDIX 5:
PRESENTATION OF INDIVIDUAL CASE HISTORIES: REPORTS FROM PATIENTS (July 2007 - June 2010)

ADR Centre No.	Date/ Year of onset	Country	Source	Age	Sex	Dosage	Treatment duration	Reaction description	SOC	PT	Outcome	Comments
[redacted]	22 May 2008	[redacted]	Consumer	Young child	F	Not relevant	Not relevant	Bit into a tube Skin redness	Injury, poisoning and procedural complications Skin and subcutaneous tissue disorders	Accidental exposure Erythema	NI	Non-serious Unlisted
[redacted]	26 Feb 2009	[redacted]	consumer	Sr	F	NI	1 treatment	Lips swelling, mouth exfoliation	Gastrointestinal disorders	Lip swelling Oral mucosal exfoliation	Swelling recovered after Benadryl.	Non-serious Unlisted
[redacted]	7 May 2008	[redacted]	Consumer	15	F	NI	NI	Allergic reaction, Trembling, rash, breathing difficulty	Immune system disorders Nervous system disorders Skin and subcutaneous tissue disorders Respiratory, thoracic and mediastinal disorders	Hypersensitivity Tremor Rash Dyspnoea	Improved after brushing teeth	Non-serious Unlisted

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[redacted]	23 Feb 2010	[redacted]	Consumer	child	M	NI	NI	Son became very hypersensitive in behavior	General disorders and administration site conditions	Irritability	NI	Non-serious Unlisted
[redacted]	02 Jun 2010	[redacted]	Consumer	Adult	F	NI	once	Felt strange after application	General disorders and administration site conditions	Feeling abnormal	Not recovered after a few days	Non-serious Unlisted

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APPENDIX 6
SUMMARY TABULATION

The below table summarizes the number of reports by terms according to the Preferred Term Level and to the System Organ Class, from the line listing of medically confirmed cases.

Terms	Serious cases		Non-serious cases		Total
	Unlisted terms – cumulative since launch	Listed terms – Mar 2007 to Feb 2010	Unlisted Terms – Mar 2007 to Feb 2010	Listed Terms – Mar 2007 to Feb 2010	
• **Gastro-intestinal disorders**	**2**	**2**	**31**	**17**	**52**
- lip swelling	-	2	-	8	10
- cheilitis	-	-	2	-	2
- oedema mouth	-	-	-	2	2
- oedema mucosa	-	-	-	1	1
- oral discomfort	-	-	3	-	3
- oral pain	-	-	1	-	1
- gingival pain	-	-	4	-	4
- gingival erythema	-	-	5	-	5
- gingival blisters	-	-	1	-	1
- gingival oedema	-	-	-	3	3
- gingivitis	-	-	-	1	1
- stomatitis	-	-	-	2	2
- mucosal inflammation	-	-	1	-	1
- oral mucosal exfoliation	-	-	2	-	2
- sensitivity of teeth	-	-	1	-	1
- tooth discolouration	-	-	1	-	1
- abdominal pain upper	-	-	2	-	2
- oesophageal pain	-	-	1	-	1
- eructation	-	-	1	-	1
- vomiting	-	-	1	-	1
- nausea	-	-	5	-	5
- paraesthesia oral	1	-	-	-	1
- swollen tongue	1	-	-	-	1
• **Immune system disorders**	**2**	**0**	**5**	**0**	**7**
- hypersensitivity	1	-	5	-	6
- anaphylactoid reaction	1	-	-	-	1
• **General disorders and administration site conditions**	**4**	**0**	**18**	**0**	**22**
- application site swelling	1	-	-	-	1
- application site pain	1	-	-	-	1
- application site irritation	-	-	12*	-	12*
- application site reaction	-	-	1	-	1
- fatigue	1	-	-	-	1
- pyrexia	-	-	2	-	2

- asthenia	1	-	-	-	1
- oedema peripheral	-	-	1	-	1
- malaise	-	-	1	-	1
- pain	-	-	1	-	1
• **Nervous system disorders**	**4**	**0**	**1**	**0**	**5**
- headache	-	-	1	-	1
- somnolence	1	-	-	-	1
- incoherent	1	-	-	-	1
- tremor	1	-	-	-	1
- dizziness	1	-	-	-	1
• **Psychiatric disorders**	**1**	**0**	**0**	**0**	**1**
-nervousness	1	-	-	-	1
• **Skin and subcutaneous tissue disorders**	**2**	**0**	**10**	**0**	**12**
- swelling face	2	-	4	-	6
- rash	-	-	1	-	1
- rash macular	-	-	1	-	1
- dermatitis	-	-	1	-	1
- acne	-	-	1	-	1
- urticaria	-	-	1	-	1
- hyperhidrosis	-	-	1	-	1
• **Eye disorders**	**0**	**0**	**1**	**0**	**1**
- eye irritation	-	-	1	-	1
• **Respiratory, thoracic and mediastinal disorders**	**0**	**0**	**4**	**0**	**4**
- pharyngeal erythema	-	-	1	-	1
- oropharyngeal pain	-	-	1	-	1
- dyspnoea	-	-	1	-	1
- throat irritation	-	-	1	-	1
• **Cardiac disorders**	**1**	**0**	**0**	**0**	**1**
- palpitations	1	-	-	-	1
• **Blood and lymphatic system disorders**	**1**	**0**	**0**	**0**	**1**
- lymphadenopathy cervical	1	-	-	-	1
• **Injury, poisoning and procedural complications**	**0**	**0**	**1**	**0**	**1**
- accidental exposure	-	-	1	-	1
TOTAL	**17**	**2**	**71**	**17**	**107**

All the terms are coming from the 51 case reports described in the line listing of Appendix 4 (from which 12* were from a same massive notification by the same dentist in the US).

APPENDIX 7

PUBLISHED LITERATURE STUDIES

- **1) Izquierdo-Vega J, Sanchez-Gutierrez M, Del Razo LM.**
  Decreased in vitro fertility in male rats exposed to fluoride-induced oxidative stress damage and mitochondrial transmembrane potential loss.
  Tox Appl Pharmacol 2008; 230: 352-357

  Summary:
  The aim of the study was to evaluate the effect of environmentally relevant doses of fluoride on in vitro fertilization (IVF) capacity of spermatozoa, and its relationship to spermatozoa mitochondrial transmembrane potential (DeltaPsi(m)). Male Wistar rats were administered at 5 mg fluoride/kg body mass/24 h, or deionized water orally for 8 weeks. Spermatozoa from fluoride-treated rats exhibited a significant decrease in superoxide dismutase (SOD) activity (~33%), accompanied with a significant increase in the generation of O(2)(-) (~40%), a significant decrease in DeltaPsi(m) (~33%), and a significant increase in lipid peroxidation concentration (~50%), relative to spermatozoa from the control group. Consistent with this finding, spermatozoa from fluoride-treated rats exhibited altered plasmatic membrane. In addition, the percentage of fluoride-treated spermatozoa capable of undergoing the acrosome reaction was decreased relative to control spermatozoa (34 vs. 55%), while the percentage fluoride-treated spermatozoa capable of oocyte fertilization was also significantly lower than the control group (13 vs. 71%). These observations suggest that subchronic exposure to fluoride causes oxidative stress damage and loss of mitochondrial transmembrane potential, resulting in reduced fertility.

- **2) Dvořáková-Hortová K, Sandera M, Jursová M, Vašinová J, Pěknicová J**
  The influence of fluorides on mouse sperm capacitation
  Anim Reprod Sci. 2007 Aug 6; : 17884311 [Epub ahead of print]

  Summary:
  Increasing infertility, due to pathological changes on sperm, has become a serious issue. Eco-toxicological effect of rising concentration of fluorides can be enhanced in the presence of aluminium ions by forming fluorometallic complexes, analogues of phosphate groups that interfere with the activity of G-proteins and P-type ATPases, which are part of several signalling pathways during sperm maturation. In order for sperm to gain fertilizing ability, they must undergo in the female reproductive tract, capacitation that includes tyrosine phosphorylation and consequent actin polymerization. The present paper reports the findings of 3-month oral toxicity in mice of fluorides at the concentrations 0, 1, 10, and 100ppm and their synergic action with aluminium at dose of 10ppm. There were no mortalities, clinical signs of discomfort or body weight loss during the experiment. The analysis revealed, for the concentrations of 10 and 100ppm, abnormalities of spermatogenesis and ability of epididymal spermatozoa to capacitate in vitro, as the result of decreased sperm head tyrosine phosphorylation and actin polymerization. The enhancing overload caused by fluorides represents a potential factor, having an impact on function of sperm, hence contributing to a growing infertility in the human population.

- **3) Chioca LR, Raupp IM, Da Cunha C, Losso EM, Andreatini R.**
  Subchronic fluoride intake induces impairment in habituation and active avoidance tasks in rats.
  Eur J Pharmacol. 2008 Jan 28;579(1-3):196-201.

  Summary
  Since clinical case reports suggest that sodium fluoride (NaF) intoxication may impair learning and memory, the objective of the present study was to evaluate the effects of NaF on two memory tasks: open-field habituation and two-way active avoidance. Adult male rats were exposed to NaF in drinking water at three concentrations for 30 days: 1.54 (control, tap water), 50 and 100 ppm NaF (corresponding to an intake of 0.10+/-0.005, 5.15+/-0.14, and 10.77+/-0.39 mg/kg of NaF, respectively). At day 30, the rats were placed in an open-field and retested after 24 h (test session) to measure habituation. In the two-way active avoidance task, another three groups of rats were trained in a 30-trial training session and tested again 24 h later (test session). Dental fluorosis was also evaluated. Habituation was impaired by 50 and 100 ppm, but not by 1.54 ppm NaF. Moreover, 100 ppm NaF reduced the number of avoidance responses in the active avoidance task. No locomotor impairment was observed. Mild dental fluorosis in rat incisor teeth was found in the 50 and 100 ppm NaF groups. Overall, these results suggest that moderate intoxication with sodium fluoride has potentially deleterious effects on learning and memory.

- **4) Bera I, Sabatini R, Auteri P, Flace P, Sisto G, Montagnani M, Potenza MA, Marasciulo FL, Carratu MR, Coluccia A, Borracci P, Tarullo A, Cagiano R.**
  Neurofunctional effects of developmental sodium fluoride exposure in rats.
  Eur Rev Med Pharmacol Sci. 2007 Jul-Aug;11(4):211-24.

  Summary
  Contrasting studies on the toxic effects of sodium fluoride (NaF) during developmental stages of Wistar rats, lead us to investigate the neurofunctional effects caused by its perinatal exposure, devoid of any overt sign of toxicity and/or gross malformation. NaF solution was administered to pregnant rats by intragastric gavage at a daily dose of 2.5 and 5.0 mg/kg from gestational day 0 to day 9 after parturition. Developmental NaF exposure caused sex and dose specific behavioural deficits which affected males more than females in the majority of the evaluated end-points. In particular, the perinatal exposure to NaF 5.0 mg/kg, significantly affected learning, memory, motor coordination and blood pressure only in male rats. Conversely, a lack of habituation upon the second presentation of the objects and failure in the ability to discriminate between the novel and the familiar object were observed only in NaF 5.0 mg/kg female rats. Finally, a significant impairment of sexual behaviour was observed in male rats at both NaF dose levels. The present data indicate that perinatal rat exposure to NaF results in long lasting functional sex-specific alterations which occur at fluoride levels approaching those experienced by offspring of mothers.

- **5) Olympio KP, Cardoso VE, Bijella MF, Pessan JP, Delbem AC, Buzalaf MA.**
  Urinary fluoride output in children following the use of a dual-fluoride varnish formulation.
  J Appl Oral Sci; 2009; 17(3):179-83.

  Summary:
  This study evaluated the bioavailability of fluoride after topical application of a dual-fluoride varnish commercially available in Brazil, when compared to Duraphat. The urinary fluoride output was evaluated in seven 5-year-old children after application of the fluoride varnishes, in two different phases. In the first phase (I), children received topical application of the fluoride varnish Duofluorid XII (2.92% fluorine, calcium fluoride + 2.71% fluorine, sodium fluoride, FGM). After 1-month interval (phase II), the same amount (0.2 mL) of the fluoride varnish Duraphat (2.26% fluorine, sodium fluoride, Colgate) was applied. Before each application all the volunteers brushed their teeth with placebo dentifrice for 7 days. Urinary collections were carried out 24 h prior up to 48 h after the applications. Fluoride intake from the diet was also estimated. Fluoride concentration in diet samples and urine was analyzed with the fluoride ion-specific electrode and a miniature calomel reference electrode coupled to a potentiometer. Data were tested by ANOVA and Tukey's post hoc test ($p<0.05$). RESULTS: There were significant differences in the urinary fluoride output between phases I and II. The use of Duofluorid XII did not significantly increase the urinary fluoride output, when compared to baseline levels. The application of Duraphat caused a transitory increase in the urinary fluoride output, returning to baseline levels 48 h after its use. The tested varnish formulation, which has been shown to be effective in *in vitro* studies, also can be considered safe.

- **6) Ekstrand K, Martignon S, Holm-Pedersen P.**
  Development and evaluation of two root caries controlling programmes for home-based frail people older than 75 years.
  Gerodontology (England); 2008; 25 (2): 67-75

  Summary:
  One of the objectives is to compare the effectiveness of two preventive programmes in controlling root caries in elderly people. Four clinical variables: texture, contour, location and colour of root caries lesions were selected to evaluate lesion activity. 215 homebound 75+ year olds were randomly assigned to one of three groups: group 1, once a month a dental hygienist brushed the teeth of the participants and applied Duraphat vanish to active root caries lesions. The participants in groups 2 and 3 received 5000 and 1450 ppm F-toothpaste, respectively, to use twice a day. This study included an interview, a baseline examination and a final follow-up examination after 8 months. Data from those 189 (88%) who completed the study disclosed that there were no inter-group differences at the baseline examination concerning relevant conditions. At the end of the study, the root caries status of participants in groups 1 and 2 had improved significantly when compared with group 3 ($p < 0.02$). No significant difference was observed between groups 1 and 2 ($p = 0.14$).

- **7) Olusile AO, Bamise CT, Oginni AO, Dosumu OO.**
  Short-term clinical evaluation of four desensitizing agents..
  J Contemporary Dental Practice ; 2008; 9 (1):22-9

Summary:
The objective is to evaluate the effectiveness of four topical desensitizing agents in providing short-term relief of dentin hypersensitivity. One hundred sixteen hypersensitive teeth with a positive response to intraoral testing for dentin hypersensitivity were included in this study. The four desensitizing agents tested were Duraphat, 2% fluoride iontophoresis, copal varnish (CV), and Gluma Comfort Bond Plus Desensitizer. Following a specific regimen randomly determined desensitizing agents were applied in an alternating order when patients presented in a clinical setting with a complaint of hypersensitive teeth. A visual analogue scale was used to determine the degrees of hypersensitivity at three points in time. The first being just before the treatment to establish a baseline, then at 24 hours post-treatment, and the last at seven days post-treatment. Differences in the mean pain scores (MPS) between the baseline and post-treatment evaluation periods were used to determine the reduction in dentin hypersensitivity. All agents caused a statistically significant reduction in dentin hypersensitivity within 24 hours of treatment. Only the reductions for iontophoresis and Gluma were statistically significant at seven days ($p<0.05$).