RVG 06269

Ref: ELG-NL-20

ELMEX® MEDICAL CARIESPROTECTIE GEL 12,5 MG/G, TANDGEL

Active ingredient: Amine Fluoride (Olafur, Dectaflur)
Sodium Fluoride

ATC Code: A01A A51

PERIODIC SAFETY UPDATE REPORT

VALID FOR THE FOLLOWING MAH:

THE NETHERLANDS	GABA B.V.	RVG 06269

PERIOD COVERED BY THIS REPORT: 01.08.2005– 31.07.2009

INTERNATIONAL BIRTH DATE
17.06.1969 (SWITZERLAND)

EU BIRTH DATE:
03.07.1969 (BELGIUM)

DATE OF REPORT: 10 SEPTEMBER 2009

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EXECUTIVE SUMMARY

elmex® gelée is a fluoride toothpaste containing 33.19 mg amine fluorides (30.32 mg olaflur and 2.87 mg dectaflur) and 22.1 mg sodium fluoride per gram of gel. This corresponds to a total fluoride content of 1.25 %.

Elmex® gelée is used topically in caries prophylaxis for the fluoridation of tooth enamel. The dental gel promotes remineralisation of initial caries and is suitable in the treatment of hypersensitive dental necks. In addition, the amine fluorides (olaflur/dectaflur) have antimicrobial properties.

elmex® gelée is commercialised in several countries. In most of the countries, elmex® gelée has an OTC status. In some countries, including The Netherlands, it is authorised as an Rx drug and in Spain as a Dentifrice.

The trade name elmex® gelée is also used in most countries with slight deviations in Finland, the Netherlands, Belgium and Austria. In the Netherlands, the trade name is "elmex® Medical Cariesprotectiegel 12,5 mg/g, tandgel".

This PSUR covers the period August 2005 up to end of July 2009.
During this period, there have been no suspensions or failure to grant renewal of the Marketing Authorisation, no change to the formulation of the product and no changes in the target population. A proposed change in the Core Company Data Sheet is explained in section 4.

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This report confirms that the overall safety profile of elmex® gelée is very good. With an exposure over [redacted] packs during the period of this PSUR, there have been 62 medically confirmed or authority issued reports of adverse reactions from which there were no serious adverse reactions.
For the non-serious reports, most of them were related to gastrointestinal disorders as could be expected for this type of product. Thirty-seven reports contained reactions that were listed, while twenty-five reports contained at least 1 unlisted reaction. However, several of them were insufficiently related to the use of the product or were isolated single cases of the type of reaction. There was thus no evidence of a specific signal that could be identified from the analysis of the cases that could lead to new relevant information linked to the risk-benefit balance of the product.

From the analysis of consumer reports, the non-medically confirmed cases concern essentially minor gastrointestinal disorders and more specifically minor reactions in the oral cavity, which can usually be expected with this type of product. Consumer reports did not provide any additional information to the ones coming from the medically confirmed cases.

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

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[redacted]

1. INTRODUCTION

This report is a Periodic Safety Update (PSU) for the stomatological agent elmex® gelée which has been commercially available for decades. This PSUR is based on the Guidance "Volume 9A of the rules governing medicinal products in the European Union – Guidelines on pharmacovigilance for medicinal products for human use, September 2008"

All ADRs have been collected and reported by the main Registration Department/Pharmacovigilance Section, or by the Medical Science Department of:

The PSUR has been reported and updated by GABA International AG

Brief introduction of elmex® gelée

Active ingredients

1g elmex® gelée contains 33.19 mg amine fluorides (30.32 mg olaflur and 2.87 mg dectaflur) and 22.1 mg sodium fluoride. This corresponds to a total fluoride content of 1.25 %.

Description of organic fluorides (amine fluorides)

Olaflur:
- [redacted]
- N,N`,N`-tris(2-hydroxyethyl)-N-octadecyl-1,3-propanediamine dihydrofluoride
- amine fluoride 297
- [redacted]

Dectaflur:
- [redacted]
- 9-octadecenylamine hydrofluoride
- amine fluoride 335
- [redacted]

Description of inorganic fluoride:

Sodium Fluoride:
- [redacted]
- PHEUR

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Excipients

formulation 447/1716 contains
water, propylene glycol, flavouring agent 1304 (dl-menthone, apple aroma, banana aroma, peppermint oil and spearmint oil), hydroxyethyl cellulose, saccharin.

This formulation is valid for all market, except the Slovenian market with formulation 447/402.
See also Table 1: Overview of formulations approved, page 7.

Indications

Caries prophylaxis, treatment of initial caries lesion, treatment of hypersensitive dental necks
See also section 2. World wide Marketing Authorisation Status.

[redacted]

Mechanism of action

Elmex® gelée is used topically in caries prophylaxis for the fluoridation of tooth enamel. The dental gel promotes remineralisation of initial caries and is suitable in the treatment of hypersensitive dental necks. The high affinity of the amine fluorides for the surface of the tooth results in accumulation of fluoride in the dental enamel. At the same time, the solubility (and therefore also the demineralisation) of the enamel is reduced. In addition, the amine fluorides olaflur/dectaflur have antimicrobial properties.

Package size

elmex® gelée is available in the package sizes of:

- 25 g (in all 20 countries, where elmex® gelée is marketed)
- 38 g (in Belgium, Curaçau, Germany and the Netherlands)
- 215 g (in Belgium, Czech Republic, Finland, Germany, Hungary, Italy, Poland and in Switzerland)

Details of the worldwide marketing authorisation status are provided in section 2.

MedDRA version 12.0 has been used for coding in this report.

2. WORLDWIDE MARKETING AUTHORISATION STATUS

elmex® gelée is commercialised in several countries. According to the date of registration of elmex® gelée, the countries where the product has been placed on the market, are listed in Appendix 1.

elmex® gelée was first marketed in Switzerland on 17.06.1969 (IBD), followed by Belgium on 03.07.1969 (EBD).

In most of the countries, elmex® gelée with the pack size of 25g has an OTC status. In some countries, i.e. Finland, Slovenia, The Netherlands and Israel, it is authorised as an Rx drug. And in Spain, elmex® gelée is registered as a Dentifrice.

The trade name elmex® gelée is used in most of the countries. A slightly deviated name is registered in Finland (elmex® dental gel), the Netherlands (elmex® medical cariesprotectiegel 12,5 mg/g, tandgel), Belgium (elmex® Medicalgel) and Austria (elmex® Dentalgel).

The indication is differently described in the SPCs. Some indications describe the therapeutic treatment and some, the mechanism of action of the active ingredients.

Country specific differences in the composition are as follows:

Finland
Due to harmonisation purposes, the formulation 447/104, which was the first developed composition of elmex® gelée, was used until the new formulation 447/1716 was approved in September 2002.
The new formulation contains no colouring agent, no preservatives agent, no abrasive agent and has a different aroma composition. For more details about composition of elmex® gelée, see section 3 on page 8.
The total fluoride concentration remains the same as 1.25 % fluoride.

Netherlands
elmex® gelée was available in the Netherlands with two different pharmaceutical dosages, a total fluoride content of 1.25 % (formulation 447/1716) and a total fluoride content of 0.4 % (formulation 447/1761).
The difference between these two formulations mainly was in the content of fluoride. The formulation 447/1716 contained about 85 % less sodium fluoride.
Due to harmonisation purposes, the registration of elmex® gelée 0.4 % fluoride, has been omitted by the MAH in 2003.
elmex® gelée with 1.25 % fluoride is still registered in the Netherlands.

Slovenia
Currently authorised formulation is 447/402, which also differs in aroma. Furthermore, it contains colouring agent and preservative agent.
Due to harmonisation purposes, formulation 447/1716 was submitted in September 2001 and approved end of 2005.

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

During the period of this PSUR, there have been no suspensions or failure to grant renewal of the Marketing Authorisation for elmex® gelée, and no restrictions to distribution . There has been no change to the formulation of the product or changes in the target population.

Before the period of this PSUR, the reasons for a change of formulation from 447/402 to 447/1716 were as following:

- *Addition of Propylene Glycol-* The viscosity of the gel has been improved by the use of propylene glycol as solvent and solvent mediator (no longer any liquefaction of the final product). Due to propylene glycol the hydrolytic activity in the aqueous system of elmex® gelée is slowed down.

- *The flavouring agent-* cinnamon oil (flavour 19B) has been replaced with flavour 1304, thus removing the allergic potential and preventing burning in the mouth. The acceptance of the flavour is thereby improved.
- *Methylparabene-* Since the Olaflur/Dectaflur combination has a preservative effect on is own, methylparaben for this purpose can be omitted. This also removes a potential cause of allergy.
- *Color C.I. 16255-* By dropping the colorant from the formula, a further allergic potential is avoided.

Table 1: Overview of formulations approved

Excipients in Formulation 447/1716 (third and current composition)	**Excipients in Formulation 447/402** (second composition developed)	**Excipients in Formulation 447/104** (first composition developed)
water flavouring agent 1304 dl-menthone apple flavour banana flavour peppermint oil spearmint oil hydroxyethyl cellulose saccharin propylene glycol	Water flavouring agent 19B menthol nature menthone synthetic banana flavour peppermint oil spearmint oil cinnamon oil hydroxyethyl cellulose saccharin methylparaben colouring agent C.I.16255	water. flavouring agent 796 menthol anise oil peppermint oil spearmint oil vanillin saccharin methyl parahydroxybenzoate (=methylparaben) sodium riboflavin phosphate sodium metaphosphate guar gum

4. CHANGES TO REFERENCE SAFETY INFORMATION

As the official local data sheets are slightly different from each other and a harmonisation of the safety information is considered, the first Core Company Data Sheet (CCDS, version 1), has been prepared on the basis of the German official safety information and on the basis of all ADRs reported in the PSUR. Within the regular internal update of the PSUR, the CCDS has been reviewed by changing the ATC code only. The new ATC code A01AA51 for sodium fluoride and combination, which is more suitable for elmex® gelée (former ATC code A01AA30 for combination of fluoride) has been introduced in version 2 of the CCDS.
The CCDS, version 3, has been changed in the format while in 2009, the following sentence has been added in version 4 of the CCDS, under the section 'Posology and method of administration – Use at home': "The total time of application (brushing and

residence time) must not exceed 5 minutes." Furthermore, additional paragraphs have been introduced to the CCDS and CCSI for the use of elmex® gel in group prophylaxis

With respect to the Company Core Safety Information (CCSI), which has been prepared for determining listed and unlisted ADR reports, it has been progressively revised to reflect the updates of the CCDS and is now available in version 5 .

The German SPC was chosen as reference SPC for other countries.

In new EU Member States such as Slovak Republic, Czech Republic and Hungary, the dossiers of all pharmaceutical products had to be updated due to EU accession. Therefore, the SPCs for elmex® gelée in the Slovak and Czech Republics and Hungary were harmonized with the German SPC in 2003.

The Belgian SPC had been adapted according to the Belgian Template for SPC and safety information had been harmonized with the German SPC in September 2004.
In 2004 the harmonization of the Dutch SPC has been submitted with approval in April 2006.
The harmonization of the Finnish SPC was submitted in 2005 and approved in 2006.

The Core Company Data Sheet is provided in Appendix 2 and the Core Company Safety Information in Appendix 3.

5. PATIENT EXPOSURE

In this PSUR, the number of the packs sold on the markets during the period of 1 August 2005 to 31 July 2009 has been used as a comparative factor for estimating the frequency of patient exposure since it is impossible to estimate the patient exposure and the daily dose for elmex® gelée. Reasons therefore are that elmex® gelée has two modes of application :

- a) tooth brushing with 1-2 cm gel (approximately 0.5 g gel) per week recommended at home or several times per month or year in group prophylaxis (e.g. school) and
- b) tray application; the dosage depends on the tray size (in general 3-8 g gel)

In total **more than [redacted] packs** of elmex® gelée have been sold between August 2005 and July 2009. More details are provided in table 2.

Table 2: Number of sold packs

Country	Total packs sold Aug-Dec 2005	Total packs sold 2006*	Total packs sold 2007	Total packs sold 2008	Total packs sold Jan-July 2009	Total Aug 05 – Jul 09
Germany	[redacted]					
Switzerland						
Austria						
The Netherlands						
Other countries**						
Total per year						
Total packs sold between August 2005 and July 2009:						

* 2006: all data were not available. Those not available were estimated based on 2005 and 2007 data.
** Other countries include: Belgium, Luxemburg, Finland, Slovak Republic, Czech Republic, Hungary, Poland, Portugal, Croatia, Slovenia, Israel, South Africa and Spain.

6. INDIVIDUAL CASE HISTORIES

6.1 General Considerations

All individual case reports meeting the criteria defined below received by GABA International during the review period are presented in the line listing (see Appendix 4).

- All serious adverse reactions regardless of the source of the information

- Non-serious unlisted adverse reactions from spontaneous reporting (patients when confirmed by a health care professional*, health care professionals, authorities), post-authorisation safety studies and literature

- Non-serious listed adverse reactions from spontaneous reporting (patients when confirmed by a health care professional*, health care professionals, authorities) and post-authorisation safety studies

Patients/consumer reports not confirmed by a health care professional are presented in a separate line listing as well as spontaneous case reports unrelated to the use of the product (causality denied by the health care professional) (see Appendix 5)

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 from a suspected 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 CCSI.

6.2 Cases Presented as Line Listing

There were no serious ADR during the period covered by this PSUR, no case coming from literature searches relevant to elmex® gelée and no case issued from clinical studies.

A line listing with all medically confirmed cases or cases reported directly by an Authority are included in the report as explained above and displayed in Appendix 4.

6.3 Overview – summary tabulation

In the period under review, there were a total of 61 individual case histories possibly (causality is not fully excluded) related to the use of elmex® gelée and reported by healthcare professionals or authorities. There were no serious cases and from the 61 non-serious cases, 36 were listed while 25 contained , at least, 1 unlisted term.
The 61 cases gave rise to a total of 133 terms to describe the symptoms, 103 were listed and 30 were unlisted.
Out of the 133 terms, 108 were related to gastrointestinal disorders, typically what would be expected for a product like elmex® gelée. A summary tabulation of the terms used in the individual case reports is presented in Appendix 6.

6.4 Analysis of Individual Case Histories

In this chapter, medically confirmed and authorities reported cases are discussed 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

There were no serious unlisted reactions prior to or during the period of this report.

6.4.2 Serious Listed Reports

There were no serious listed reactions during the period of this report.

6.4.3 Non-Serious Unlisted Reports

In the reporting period of this PSUR, 25 non-serious case reports with at least one unlisted, symptom were reported by health care professionals or competent authorities.

a) Most of these cases (17 out of the 25) were related to Gastrointestinal Disorders

- 1 case [redacted] reported a burning sensation in the oesophagus causing coughing after swallowing. The reaction lasted a few days and resolved. This was an isolated case of oesophageal irritation.

- 2 cases of irritation of the oral cavity were reported. The first case ([redacted] lacked sufficient documentation to relate the event with certainty to the use of the product, while in the second case ([redacted] loss of taste and cracks on the tongue were reported but, in association with misuse of the product (exaggerated application time -15minutes with a tray- without rinsing).

- 1 case [redacted] reported stomach ache and headache which were not listed. However, it was also noted that the patient experienced nausea and vomiting. The case was possibly related to the use of elmex® gelée as being reported by a dentist, but information was insufficient to clearly confirm the relatedness with the product.

- 2 cases ([redacted] and [redacted]) reported some pain in the oral cavity (gums, teeth).

- There were a few cases reporting a discolouration in the oral cavity after using the product. However, none of these cases could provide sufficient evidence of a causal relationship with the product and most of them had different forms: stains on gums [redacted] unspecified mouth discolouration [redacted] white spots or discolouration of teeth ([redacted]), unspecified tooth discolouration with no indication on the usage habits [redacted] tongue/gum discolouration ([redacted]), oral mucosal discolouration [redacted] prosthesis discolouration ([redacted]

b) Cases related to other System Organ Classes

- 1 case [redacted] concerned a patient who was found unconscious after the use of elmex gelee. As the reason for the unconsciousness could not be precisely identified, the case was reported 'possibly related' although it was considered by the MAH that, based on the dosage and duration of use of the product, it was unlikely that elmex® gelée would be the cause of the reaction. The case was

further classified as a potential hypersensitivity reaction with a more detailed description in section 6.4.4. (non-serious listed reactions).

- 1 case [redacted] reported, due to incorrect application, a chemical burn around the nails of the toes (off label use)

- 1 case [redacted] reported dizziness and eye disorders (blurred vision) after applying the product with a custom made mould and not rinsed after 5 minutes. The pharmacist also reported that the product had been overdosed by the patient. It was unclear if the case could be related to the use of the product.

- 3 cases reported skin reactions after use of the product, such as contact dermatitis ([redacted]), urticaria with oedema of face and mouth [redacted] and burning and swelling of the face [redacted]). The two first cases were considered as allergic reactions related to the use of the elmex® gelée after a positive patch test.

- 1 isolated case in 2005 [redacted]) reported muscle pain after using the product, but the reaction could not clearly be related to the use of the product.

6.4.4 Non-Serious Listed Reports

There were 36 reports of non-serious listed adverse drug reactions during the period of this PSUR.

Most of them are related to minor reactions in the oral cavity and are sufficiently described in the line listing. The symptoms of most of these reactions appeared locally, with mainly some burning sensation in the oral cavity, local signs of moderate irritation (localized swelling or reddening of the mucosa, blisters,etc) resolving by themselves after stopping the product. Six cases were also noted where the consumer reported some nausea after using the product.

Four cases of allergic reactions ([redacted]) and 1 case of urticaria [redacted] were also observed as could be normally expected for an exposure occurrence of [redacted] A One of those cases [redacted] was related to a child (12 years) found unconscious after having used the product for 1 week instead of his usual toothpaste. As a precaution, he received a treatment with calcium at the hospital in case the event was caused by fluorosis, and he left after the treatment (no stationary hospitalization). The MAH calculated the maximum dose of fluoride that could have passed into the circulation in that period and estimated that after 1 week of use of elmex® gelée, it is highly unlikely that unconsciousness could have been induced by fluorosis. The physician then concluded that the reaction might have been due to a hypersensitivity reaction, but without any further confirmation. The MAH believes the reaction was unrelated to a fluorosis. However, as the causal relationship of the product can not be ruled out for hypersensitivity, the case is assessed as possibly related to the product. The case was also described with the non-serious unlisted reactions (6.4.3) due to the unconsciousness.

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6. 5 All Death Cases

No fatal cases related to the use of elmex® gelée were reported during the period under review.

7. STUDIES

7.1 Newly analyzed Company-Sponsored Studies

There have been no sponsored safety studies on elmex® gelée, relevant to the safety assessment of the product, carried out during the period under review.

However, one efficacy study (P305-R-EG04) started in 2006 is due to finish the end of 2009. This study aims at establishing the efficacy of elmex® gelée by preventing white spot lesions in patients wearing fixed orthodontic appliances. The study is run at 2 locations, Germany and Israel, on a panel of 314 healthy volunteers, and products (elmex® gelée or placebo) were applied for a period of 12 to 30 months. At the time of the datalock point (DLP) of this PSUR, the study is still in progress. Four serious adverse events have been reported but the relatedness with the tested products was clearly denied by the main investigator. There was no safety concern arising from that study at the DLP.

7.2 Targeted New Safety Studies

There are no safety studies planned on elmex® gelée.

7.3 Published Safety Studies

A search has been carried out 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.

There were no publications related to elmex® gelée or to amine fluoride. Five publications providing relevant safety information to the safety of sodium fluoride, have been considered.

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

None of the published studies raised any safety concern to elmex® gelée.

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

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, no relevant new information that might affect the interpretation or evaluation of existing reports has come to our knowledge.

8.1. Lack of efficacy

No cases of lack of efficacy were referred to us during the period of this report.

8.2. Late breaking information.

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

8.3 Risk Management Plan

No Risk management Plan is in place for this product.

8.4 Risk-Benefit Analysis Report

No specific risk-benefit analysis has been conducted on this product for which we receive only very sporadic case reports.

9. OVERALL SAFETY EVALUATION

The information gathered during the period of review is principally consistent with the established safety profile of elmex® gelée.

9.1 Cumulative Perspective: Serious Unlisted Reactions

There were no serious unlisted adverse reaction before or during the period of this report.

9.2 Cumulative perspective: Non-Serious Unlisted Reactions

There were 25 non-serious unlisted case reports during the reporting period and 30 unlisted preferred MedDRA terms. One of these terms appeared 7 times, "tooth discolouration" while all others appeared only once. For all of them, this represents a low occurrence rate of respectively 1 case per more than [redacted] (for tooth discolouration) and 1 per more than [redacted] Furthermore, for tooth discolouration that appeared 7 times, the imputability of the reaction to the use of elmex® gelée cannot be established with certainty and took different reported forms (e.g., white spots, yellow stain, coloured spots).

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9.3 Increased Reporting Frequency of listed Reactions

There were 36 non-serious listed case reports during the reporting period and 103 listed preferred MedDRA terms. The listed reaction terms which appeared the most are: oral discomfort (13 times), oedema mouth (9 times), stomatitis (8 times), oral mucosal exfoliation (7 times), and gingival pain (6 times). The occurrence rate for such minor reactions in the oral cavity is considered as remaining very low with, for the most frequent one, 1 report of oral discomfort per more than [redacted] of elmex® gelée sold.

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Nausea was also reported 6 times and hypersensitivity 4 times. However, for listed reactions, this remains at a low frequency with less that 1 report per [redacted] of product.

9.4 Changes in Characteristics of listed Reactions

None of the unlisted reactions observed during the reporting period may be considered as a signal requiring a change in the list of potential undesirable effects as they were either isolated cases and/or insufficiently related with certainty to the use of elmex® gelée. Nevertheless, tooth discolouration appeared 7 times in the 5 year period of this report and 2 times in unconfirmed consumer reports. The occurrence rate for a reaction that was not related to the use of the product with sufficient certainty is still low, but requires us to monitor its occurrence rate until the next PSUR.

9.5 Interactions

There were no reports of concomitant medications that are suspected to have interacted with elmex® gelée for causing the observed reactions.

For one of the reports [redacted] the patient was simultaneously treated for osteoporosis and for a cancer. However, the observed reaction was listed and similar to several other cases without concomitant medication. An interaction with the medication is unlikely the cause of the reaction.

9.6 Experience with overdose

There were two reported cases of overdose of the product, one with the patient having used 3 times the recommended dose and having presented with irritation in the oral cavity [redacted] and one for which the pharmacist reported it had been overdosed and used for 15 minutes with a custom made dental mould without rinsing. The patient presented with dizziness and blurred vision [redacted] but the causal relationship with the product was not clearly established.

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9.7 Abuse and misuse

There were a few reports in which the product was applied for a longer period than described in the SPC. The Core Company Data Sheet has been updated to make clearer that the product should not be used for more than 5 minutes.

One case [redacted] was also reported with a patient who did not rinse the product after having applied it for 15 minutes with a dental bar. She developed several signs of irritation in the oral cavity which resolved by themselves after withdrawal of the product.

C [redacted]

9.8 Experience with pregnancy and lactation

There were no reports of drug reaction on 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	2
Adolescent	12 – 16 years	6
Adults	17 – 64 years	24
Seniors	65 years and more	3
Not indicated		26

Gender	Number
Male	18
Female	31
Not indicated	12

In more than 40 % of the reports, the patient did not provide his/her age. For the cases where the age of the patient is indicated, 2 were on children (6 and 9 years), 6 on adolescents, 24 on adults and 3 on elderly patients.

The two cases on children were a case of allergic reaction with localized reaction in the oral cavity and one case of mucosal discolouration.
The six cases on adolescent were: 3 cases of glossodynia, 1 of nausea, 1 of tooth discolouration and 1 of loss of consciousness. Glossodynia appeared more in this patient group than in the other populations. However, the percentage remains low for a reaction in the oral cavity for this type of product.
On elderly patients, they were cases of irritation in the oral cavity with some reddening or swelling in the oral cavity, all being listed reactions .

In terms of the distribution of the reactions between patients gender, there were more reported cases on women than on men.

Overall, reactions on these patient groups did not provide any specific signal to take into account for the risk-benefit assessment in specific patient populations.

9.10 Effects of long-term treatments

One subject reported having used the product for 2 years, but less than once a week, while others reported using it many years for tooth brushing, which is quite usual for a toothpaste. The types of reactions that they reported do not seem to be related to the length of use.

9.11 Cases from non-health care professionals

Fifty-six (56) spontaneous reports were collected directly from consumers/patients during the period of this report. Most of them concern gastrointestinal disorders (49 reports) as could be expected for a toothpaste. As usually expected for consumer/patient reports, most of them do not provide sufficient evidence of a direct causal relatedness with the use of the product.

Consumer reports do not bring any new information to the safety assessment of elmex® gelée.

A line listing of the spontaneous consumer reports is given in Appendix 5 .

9.12 Prescription errors/medication errors

There were no cases of prescription error during the period of the report.

10. CONCLUSIONS

The experience gained during the period covered by this report confirms the established good safety profile of elmex® gelée.

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

APPENDIX 1 - Worldwide Marketing Authorisation Status

Country	Register-No.	Date of registration	Date of last renewal	Regulatory Status: Drug	MAH	Trade Name	Indications
Switzerland	34916 (02/039) 34916 (02/047)	17.06.1969 14.09.1995	Application 7.3.2008	25 g tube: OTC 215 g tube: OTC	GABA International AG	elmex® gelée	1. Caries prophylaxis 2. Adjunctive treatment of initial caries 3. Treatment of hypersensitive dental necks
Germany	6169101.00.00 former E 1082	18.12.1970	11/2004 ongoing	25 g tube: OTC 38 g, 215g tube: Rx	GABA GmbH	elmex® gelée	See above, Switzerland
The Netherlands	RVG 06269 RVG 09027	18.07.1973 01.04.1982	27.10.2006 05.10.1999 registration withdrawn	38 g tube: Rx 25g tube: OTC Formula 447/1761	GABA B.V.	elmex® medical cariesprotectie gel 12,5 mg/g, tandgel	1. High caries activity 2. Enamel decalcification under removable splints, partial prostheses and orthodontic appliances 3. Refluoridation of damaged enamel
Finland	6737	20.03.1974	12.2.2008	25 g Tube: Rx 215 g tube : Rx	GABA GmbH	elmex® dentaaligeeli	1. Prevention of caries 2. Treatment of hypersensitive teeth necks 3. In cases of increased risk of caries, as for instance in case of enamel damages, in persons with detachable denture prosthesis, bridges or fixed orthodontic equipments or when polishing naked enamel surfaces for filling or in connection to prosthetic measures
Curacau	80.00.009	19.02.1980	29.03.2006	38 g: tube Rx	GABA B.V.	elmex® gelée	See Switzerland, p.5
Croatia	UP/I-530-09/05-02/99	10.12.1980	27.01.2005 registration withdrawn in June 2009	25 g tube: OTC	Belupo Ltd.	Aminfluorid zele	1. Dental caries prophylaxis 2. Caries proneness (rampant caries in children older than 6 years, under the adult supervision) 3. Enamel decalcification under removable splints, partial protheses and orthodontic appliances 4. Sensitive tooth necks

Country	Register-No.	Date of registration	Date of last renewal	Regulatory Status: Drug		Trade Name	Indications
Slovenia	4-120-025	1980 Yugoslavia	24.10.2005	25 g tube: Rx	Belupo Ltd.	elmex® gelée	See above, Croatia
Spain	263-Dent	09.02.1981	06/2002 application ongoing	25 g tube: Dentifrice	GABA GmbH	elmex® gel	1. Dental caries prophylaxis 2. Enamel decalcification under removable splints, partial protaheses and orthodontic appliances 3. Sensitive tooth necks
Czech Republic	95/006/82-S C	28.01.1982	15.05.2002	25 g tube: OTC 215 g tube: Rx	GABA GmbH	elmex® gelée	1. Prevention of dental caries and the fluoridation of tooth enamel 2. Treatment of incipient caries lesions (remineralisation) 3. Treatment of hypersensitive teeth
Slovak Republic	87/0006/82-S	28.01.1982	31.01.2003	25 g tube: OTC	GABA GmbH	elmex® gelée	See Switzerland, p.5
Israel	064 99 21609 00	30.06.1982	8.8.2004	25 g tube: Rx	Teva Pharmaceutical Industrie Ltd.	elmex® gelée	1. Routine prophylaxis against caries, individual and collective. 2. Cases with a high tendency for caries. 3. Treatment of sensitive dental necks
Belgium	1362 LC 1 F7	24.09.1982	29.09.2004	25 g tube: OTC 38 g tube: OTC 215 g: Rx (hospital)	GABA B.V.	Gel médical elmex®	1. Dental caries prophylaxis 2. Partial prostheses and orthodontic appliances 3. Treatment of hypersensitive dental necks
Luxembourg	311/78/01/0775.92	07.07.1983	24.10.2002	38 g: Rx 215 g: Rx	GABA GmbH	elmex® gelée	See Switzerland, p.5
South Africa	X596	1986	No specific date	25 g tube: OTC	Dental Warehouse (distributor)	elmex® gelée	See above, Czech Rep.

Country	Register-No.	Date of registration	Date of last renewal	Regulatory Status: Drug	MAH	Trade Name	Indications
Austria	1-18093	03.06.1986	Renewal not compulsory, unless requested by MAH	25 g tube: OTC	Gebro Pharma GmbH	elmex® Zahngel	1. Treatment of initial caries lesions (after the remaining teeth have erupted) in conjunction with dietary advice and oral hygiene 2. Surface mineralisation of sensitive dental necks 3. Decalcification of enamel underneath removable bridges, 4. Refluoridation of worn sections of enamel 5. Selective grinding and dental enamel lesions
Italy	0264870 13 0264870 25	19.06.1987	05/2005 ongoing	25 g tube: Categoria C (without prescription) 215 g tube: Rx	GABA Vebas srl.	elmex® gel	1. Caries prophylaxis; hypersensitivity of dental necks 2. Decalcification of dental enamel caused by removable splints, partial protheses and orthodontic appliances 3. Refluoridation of dental enamel
Poland	590999006761 P 590999006762 P 590999033498P	21.06.1990 22.12.2000 22.7.2005	12.2.2008 12.2.2008	25 g tube: OTC 215 g tube: OTC 38g tube: OTC	GABA GmbH	elmex® zél	See Switzerland., p.5
Hungary	OGY-T-1646/01 OGY-T-1646/02	03.07.1991	27.6.2007	25 g tube: OTC 215 g tube: OTC	Teva Hungary Ltd.	Elmex®® gelée	See Czech Rep., p. 6
South Korea	NIH 1038-15509	28.09.1994	No specific date or period	25 g tube: OTC		elmex® gelée	See Switzerland, p.5
Portugal	2523397	31.10.1996	31.10.2006	25 g tube: OTC	GABA GmbH	elmex® gel	1. caries prophylaxis 2. Hypersensitivity

Appendix 2 - Company Core Data Sheet (CCDS)

1. NAME OF THE MEDICINAL PRODUCT

elmex® gelée, dental gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients, qualitative and quantitative

1g elmex® gelée contains:

Amine fluoride:

Dectaflur	2.87 mg
Olaflur	30.32 mg
Sodium fluoride	22.10 mg

This corresponds to a fluoride content of 1.25%.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Dental gel

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis
For caries prophylaxis as well as patients with dental braces, other orthodontic appliances and partial prostheses.

Therapy
Adjunctive treatment of initial caries; and treatment of hypersensitive dental necks.

4.2 Posology and method of administration

Method and duration of use

To be applied on the teeth.

Use at home

Apply elmex® gelée to a toothbrush and brush the teeth. Rinse after 2 to 3 minutes. Best used in the evenings just before going to sleep. For targeted treatment of hypersensitive dental necks, elmex® gelée is applied to the affected surface. elmex gelée should not be used before foam can be spat out. The total time of application (brushing and residence time) must not exceed 5 minutes.

Professional use

elmex® gelée is used with an appropriate gel carrier (miniplast splints or spoon applicators) or applied directly to the masticatory surfaces and interdental spaces with the blunt cannula of a filled disposable syringe.
Adequate contact time of the dental gel with the teeth (at least 2 to 4 minutes) must be maintained. Do not, however, exceed 5 minutes. Rinse out the mouth after use.

Use at school

Elmex® gelée is a suitable fluoridation preparation for class by class tooth cleaning in the context of school dental prophylaxis. Frequency of application is to be aimed by organisational factors and should be in the range 2-4 times a month. The method of application is described above.
For target application in the case of hypersensitive dental necks elmex® gelée should be applied to the relevant tooth surfaces with a soft brush and gently rubbed in.

Dosage

The following dosage may be increased in times when there is a greater risk of caries and for the treatment of hypersensitive dental necks. This applies particularly to patients with orthodontic appliances.
The following doses are recommended:

Use at home

Once a week, use about 1-2 cm elmex® gelée (approx. 0.5 g dental gel corresponding to 6.25 mg fluoride).

Use in the dental practice

Use elmex® gelée about twice a year as part of dental treatment or in individual caries prophylactic activities, or more often in high-risk patients:
- in miniplast splints approx. 3 g elmex® gelée, corresponding to approx. 37.5 mg fluoride;
- in spoon applicators up to 8 g elmex® gelée, corresponding to up to 100 mg fluoride;

- with the blunt cannula of a filled disposable syringe, apply directly to the masticatory surfaces and inter dental spaces (0.5 to 1 g elmex® gelée, corresponding to 6.25 to 12.5 mg fluoride).

Spoon application is indicated from 8 years of age.

Use in the group prophylaxis

Brush the teeth with elmex® gelée as part of group prophylactic activities about twice a year and in case of children and adolescents with increased risk of caries more often. Rinse after 2 to 3 minutes. The total time of application (brushing and residence time) must not exceed 5 minutes

4.3 Contraindications

elmex® *gelée* must not be used in cases of:

- hypersensitivity to any one of the components;
- pathological desquamative changes of the oral mucosa (erosion of the epithelium).

4.4 Special warnings and special precautions for use

As children lack control over the swallowing reflex elmex® gelée is not suitable for use in children under six years of age.

For people in whom control of the swallowing reflex cannot be guaranteed (e.g. pre-school children, disabled persons), alternatives with precise dosage, such as fluoride tablets, are to be preferred.

Systemic supplies of fluoride (e.g. with fluoride tablets) should be stopped for a few days after the application of elmex® *gelée*.

Due to the risk of overdose and subsequent intoxication the application of elmex® gelée in the Miniplast tray or with a suitably moulded wax tray is not recommended in children under eight years of age.

elmex® gelée should not be used in case of bone and/or enamel fluorosis.

Desquamation, superficial erosions and ulceration of the oral cavity mucosa have rarely (<1/10.000, including reported individual cases) been reported following spoon applications repeated after short intervals (see also 4.8)

Incompatibilities exist with anionic tensides and other large anionic molecules, all soluble calcium, magnesium and aluminium salts (see also 4.5)

4.5 Interaction with other medicinal products and other forms of interaction

The ingestion of calcium, magnesium (e.g. milk) and aluminium (in medicines for the treatment of stomach problems; antacids) immediately following treatment with elmex® *gelée* may reduce the effects of the fluorides.

4.6 Pregnancy and lactation

There is no evidence that fluorides constitute a risk to the embryo.
Fluorides pass into breast milk. elmex® *gelée* should therefore be used with caution in nursing mothers.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

Skin and subcutanous tissue disorders

In individual cases

- Desquamative changes in the oral mucosa (in very rare cases,<1/10.000, including reported individual cases)
- Superficial erosions and ulceration of the oral cavity mucosa following spoon applications repeated after short intervals.
- Hypersensitivity, intolerance, allergy reactions
- Gastrointestinal disorders

- Vomiting, nausea and diarrhoea

In case of overdose, see also 4.9 Overdose

For detail information, please refer to the CCSI.

4.9 Overdose

a) Symptoms of overdose

acute:

Local irritation of the mucosa is possible in cases of acute overdosage.

Depending on the dose and method of application, in extreme cases (e.g. with spoon application) up to 100 mg fluoride, corresponding to 8 g elmex® *gelée*, may be introduced into the oral cavity. Swallowing this amount may give rise to nausea, vomiting and diarrhoea. In most cases, these symptoms occur within the first hour after ingestion and resolve within three to six hours.

chronic:

Regularly exceeding a total daily fluoride dose of 2 mg during the development of the teeth up to approximately 8 years of age may lead to disturbances in the mineralisation of the dental enamel. This condition, known as dental fluorosis, no longer occurs after this age, even at high daily doses. It appears as flecks on the dental enamel.

b) Management of overdosage

acute:

With mild symptoms of intoxication (less than 150 mg fluoride, corresponding to less than 12 g elmex® *gelée*) calcium-containing drinks (milk, soluble calcium tablets) should be given to bind the fluoride.

With severe symptoms of intoxication (more than 150 mg fluoride, corresponding to more than 12 g elmex® *gelée*) the additional administration of activated charcoal is recommended. If necessary, calcium may be given intravenously, forced diuresis with alkalinisation of the urine may also be initiated. Heart rate, coagulation, electrolyte and acid-base balance should be monitored carefully.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Agent for caries prophylaxy
ATC code: A01A A51

The caries protection and therapeutic effects of fluorides can be attributed to three factors:

1. The increase in acid resistance of the dental enamel.
2. Inhibition of sugar breakdown by acid-producing micro-organisms in dental plaque.
3. Promotion of the remineralisation of initial carious lesions.

In amine fluoride containing compounds, the cation strengthens the caries protection and therapeutic effects. Polarisation between the hydrophobic long-chain alkyl residues and the hydrophilic amine groups confers surfactant properties to the cation. In particular, these are:

1. Longer retention time of the fluoride in the oral cavity.

2. Wetting of the clinical crown of the tooth.

3. Good ability to react with the dental enamel, which allows chemical changes to take place after only seconds:
incorporation of fluoride into the enamel (stable fluoride reservoir) and formation of a labile fluoride reservoir (calcium fluoride coating layer).

4. Marked affinity to dental plaque, which leads to slightly raised fluoride concentrations and in particular to a longer retention time of fluoride in the plaque.

5. Antimicrobial properties.

6. Inhibition of bacterial sugar breakdown to acids, lasting several hours.

7. Improved adherence of the fluoride-rich coating layer on the enamel surfaces, which can be seen in an increased acid resistance.

Treatment of initial enamel lesions through remineralisation of already decalcified areas of enamel (incipient caries) is improved by the presence of fluoride ions, in that more phosphate and calcium from the saliva are again deposited in the partially demineralised enamel. This reaction is very effectively promoted through the amine fluoride contained in elmex® *gelée*, which remains on the tooth surfaces for a long time.

For caries prophylaxis and adjunctive treatment of initial caries, the formation of a very fluoride-rich, adherent yet adequately labile coating layer is of particular importance, so that the fluoride ions may be released over weeks or even months in concentrations such as those found after the consumption of fluoridated drinking water.

Elmex® *gelée* also forms a calcium-fluoride coating layer on exposed dentine, which covers or obliterates the openings of the dentinal tubules. This protective film prevents the transmission of external stimuli from the oral cavity, thus desensitising the hypersensitive dental necks. Pain relief is not permanent and the desensitisation must be repeated as required.

5.2 Pharmacokinetic properties

Fluoride concentration profiles in the serum following topical application of fluoride-containing dental gels differ from the concentrations seen after ingestion, i.e. oral doses not coming into contact with the tissues of the oral cavity.

Depending on the mode of application (toothbrush, use of miniplast splints or spoon applicators), the retention capacity of the dentition (affected by positioning, dentures, salivary flow), material-specific characteristics (adhesiveness, surface affinity) as well as further individual factors (e.g. consumption of food and drink) the fluoride retained in the oral cavity after topical application is desorbed from its site, swallowed and

absorbed in varying amounts at different times. It is therefore not possible to obtain data on the time and intensity of peak concentrations.

The pharmacokinetic properties of orally administered fluorides are well researched. At low pH values, fluoride is converted into non-dissociated HF molecules which are rapidly absorbed. Fluoride is quickly and completely absorbed from the small intestine. The peak plasma concentration is achieved within 30 minutes. Plasma half-life is about three hours (1.5 – 5 hours). Fluoride is mainly eliminated via the kidneys. Very small quantities (insoluble calcium salts) are excreted in the faeces. The greater the rate of diuresis and the greater the alkalinity of the urine, the faster the rate of renal excretion of fluorides. Fluorides are released in the saliva and re-absorbed in the gastrointestinal tract. Fluorides are also excreted in breast milk.

Fluoride is a naturally-occurring component of the body and is found in bones and the hard substances of the teeth.

5.3 Preclinical safety data

No additional information is available from the preclinical studies which has not already been mentioned.
With correct use of elmex® *gelée* there is no risk of toxic serum fluoride concentrations being reached.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water, propylene glycol, hydroxyethylcellulose, saccharin, apple flavour, peppermint oil, spearmint oil, menthone flavour, banana flavour

6.2 Incompatibilities

See capital 4.4 'Special warnings and precautions for use'

6.3 Shelf life

3 years

After opening the container, the medicinal product is to be used until the end of the expiry date.

6.4 Special precautions for storage

Do not store over 25°C

6.5 Nature and contents of container, package sizes

25g tube: Polyethylene laminate stand tube with a child-proof closure.
38g and 215g tube: Polyethylene laminate stand tube.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Corporate Headquarter: GABA International Ltd.
Grabetsmattweg, CH-4106 Therwil, Switzerland

8. MARKETING AUTHORISATION NUMBER(S)

See List of World Wide Marketing Authorisation, in section 2 of the PSUR.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

See List of World Wide Marketing Authorisation, in section 2 of the PSUR.

10. DATE OF REVISION OF THE TEXT

Version 4

Therwil, 17.July.2009

Appendix 3 - Company Core Safety Information (CCSI)

The CCSI forms the basis for determining whether an adverse drug reaction is already listed or still unlisted in relation with the medicinal product mentioned below.

DETERMINATION OF LISTED AND UNLISTED ADVERSE DRUG REACTIONS

Listed ADRs:
Reported ADRs are already described in the CCDS and in the official product information (EU SPCs or locally approved product information). These ADRs are expected in association with the drug.

Unlisted ADRs:
An ADR whose nature, severity, specificity or outcome is not consistent with the information included in the CCSI. Unlisted ADR is interpreted as unexpected ADR with reference to the SPCs.

1. NAME OF THE MEDICINAL PRODUCT

elmex® gelée, dental gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1g elmex® gelée contains:

Dectaflur (Amine fluoride) 2.87 mg, Olaflur (Amine fluoride) 30.32 mg and Sodium fluoride 22.10 mg.

This corresponds to a fluoride content of 1.25 %.

Excipients:
Purified water, propylene glycol, hydroxyethylcellulose, saccharin, apple flavour, peppermint oil, spearmint oil, menthone flavour, banana flavour

3. PHARMACEUTICAL FORM

Dental gel

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis

Caries prophylaxis, especially in children and adolescents, as well as patients with dental braces, other orthodontic appliances and partial prostheses.

Therapy

Adjunctive treatment of initial caries

Treatment of hypersensitive dental necks

4.2 Posology and method of administration

Method and duration of use

To be applied on the teeth.

Use at home
Apply elmex® gelée to a toothbrush and brush the teeth. Rinse after 2 to 3 minutes. Best used in the evenings just before going to sleep.

For targeted treatment of hypersensitive dental necks, elmex® gelée is applied to the affected surfaces. elmex gelée should not be used before foam can be spat out.

The total time of application (brushing and residence time) must not exceed 5 minutes.

Professional use
elmex® gelée is used with an appropriate gel carrier (miniplast splints or spoon applicators) or applied directly to the masticatory surfaces and interdental spaces with the blunt cannula of a filled disposable syringe.

Adequate contact time of the dental gel with the teeth (at least 2 to 4 minutes) must be maintained. Do not, however, exceed 5 minutes. Rinse out the mouth after use.

Use at school
Elmex® gelée is a suitable fluoridation preparation for class by class tooth cleaning in the context of school dental prophylaxis. Frequency of application is to be aimed by organizational factors and should be in the range 2-4 times a month. The method of application is described above.
For target application in the case of hypersensitive dental necks elmex® gelée should be applied to the relevant tooth surfaces with a soft brush and gently rubbed in.

Dosage

The following dosage may be increased in times when there is a greater risk of caries and for the treatment of hypersensitive dental necks. This applies particularly to patients with orthodontic appliances.
The following doses are recommended:

Use at home

Once a week, use about 1-2 cm elmex® gelée (approx. 0.5 g dental gel corresponding to 6.25 mg fluoride).

Use in the dental practice

Use elmex® gelée about twice a year as part of dental treatment or individual caries prophylactic activities, or more often in high-risk patients:
- in miniplast splints approx. 3 g elmex® gelée, corresponding to approx. 37.5 mg fluoride;
- in spoon applicators up to 8 g elmex® gelée, corresponding to up to 100 mg fluoride;
- with the blunt cannula of a filled disposable syringe, apply directly to the masticatory surfaces and interdental spaces (0.5 to 1 g elmex® gelée, corresponding to 6.25 to 12.5 mg fluoride).

Spoon application is indicated from 8 years of age.

Use in the group prophylaxis

Brush the teeth with elmex® gelée as part of group prophylactic activities about twice a year and in case of children and adolescents with increased risk of caries more often. Rinse after 2 to 3 minutes. The total time of application (brushing and residence time) must not exceed 5 minutes.

4.3 Contraindications

elmex® gelée must not be used in cases of:

- hypersensitivity to any one of the components;
- pathological desquamative changes of the oral mucosa (erosion of the epithelium).

4.4 Special warnings and special precautions for use

As children lack control over the swallowing reflex elmex® gelée is not suitable for use in children under six years of age.

For people in whom control of the swallowing reflex cannot be guaranteed (e.g. pre-school children, disabled persons), alternatives with precise dosage, such as fluoride tablets, are to be preferred.

Due to the risk of overdose and subsequent intoxication the application of elmex® gelée in the Miniplast tray or with a suitably moulded wax tray is not recommended in children under eight years of age.

elmex® gelée should not be used in case of bone and/or enamel fluorosis.

Systemic supplies of fluoride (e.g. with fluoride tablets) should be stopped for a few days after the application of elmex® gelée.

Desquamation, superficial erosions and ulceration of the oral cavity mucosa have rarely (<1/10.000, including reported individual cases) been reported following spoon applications repeated after short intervals

Incompatibilities exist with anionic tensides and other large anionic molecules, all soluble calcium, magnesium and aluminium salts.

4.5. Interaction with other medicinal products

The ingestion of calcium, magnesium (e.g. milk) and aluminium (in medicines for the treatment of stomach problems; antacids) immediately following treatment with elmex® gelée may reduce the effects of the fluorides.

4.6. Pregnancy and lactation

There is no evidence that fluorides constitute a risk to the embryo.
Fluorides pass into breast milk. elmex® gelée should therefore be used with caution in nursing mothers.

4.7. Effects on ability to drive and use machines

Elmex® gelée has no influence to drive and use machine.

4.8. Undesirable effects

In very rare cases (<1/10.000, including reported individual cases), desquamative changes in the oral mucosa may occur.

Hypersensitivity reactions cannot be ruled out.

Desquamation, superficial erosions and ulceration of the oral cavity mucosa have rarely (<1/10.000, including reported individual cases) been reported following spoon applications repeated after short intervals.

4.9 Overdose

a) Symptoms of overdose

Acute:

Local irritation of the mucosa is possible in cases of acute overdosage.

Depending on the dose and method of application, in extreme cases (e.g. with spoon application) up to 100 mg fluoride, corresponding to 8 g elmex® gelée, may be introduced into the oral cavity. Swallowing this amount may give rise to nausea, vomiting and diarrhoea. In most cases, these symptoms occur within the first hour after ingestion and resolve within three to six hours.

Chronic:
Regularly exceeding a total daily fluoride dose of 2 mg during the development of the teeth up to approximately 8 years of age may lead to disturbances in the mineralisation of the dental enamel. This condition, known as dental fluorosis, no longer occurs after this age, even at high daily doses. It appears as flecks on the dental enamel.

b) Management of overdosage

Acute:
With mild symptoms of intoxication (less than 150 mg fluoride, corresponding to less than 12 g elmex® gelée) calcium-containing drinks (milk, soluble calcium tablets) should be given to bind the fluoride.

With severe symptoms of intoxication (more than 150 mg fluoride, corresponding to more than 12 g elmex® gelée) the additional administration of activated charcoal is recommended. If necessary, calcium may be given intravenously, forced diuresis with alkalinisation of the urine may also be initiated. Heart rate, coagulation, electrolyte and acid-base balance should be monitored carefully.

4.10. Undesirable effects –Listed ADRs

NON SERIOUS LISTED Adverse Drug Reactions

Organ class (MedDRA)	**Adverse term (LLT)**	MAH assessment
Respiratory, thoracic and mediastinal disorders	Asthma	Allergy/hypersensitivity
Gastrointestinal disorders	Mouth: burning/swelling/reddening/itching/ blisters	Allergy/hypersensitivity
	Mouth: erosion, irritation	Irritations
	Mouth: desquamation	Irritations
	Mouth: strong aching, exfoliation of oral mucosa	Hypersensitivity, irritation
	Mouth: scaling of the gum and oral mucosa	Hypersensitivity, irritation

	Mouth: inflammation	Allergy/hypersensitivity
	Mouth: dryness	Other
	Mouth: ulcerous, blisters, aphthae	Allergy/hypersensitivity
	Mouth: stomatitis	Allergy/hypersensitivity
	Mouth: gingivitis	Allergy/hypersensitivity
	Mouth: wound and pimples	Irritations
	Mouth: taste irritated	
	Tongue: numbness	Allergy/hypersensitivity
	Tongue and gums: swelling	Allergy/hypersensitivity
	Vomiting, nausea, sickness	Due to wrong application/intake/ other
Skin/subcutaneous tissue disorders	Skin: redness, swelling, blisters	Allergy/hypersensitivity
	Lips: erosion	Irritation

5. DATE OF REVISION OF THE TEXT

Version 5
Therwil, 17.07.2009

Corporate Headquarter: GABA International AG, Switzerland

APPENDIX 4
LINE LISTING OF MEDICALLY CONFIRMED AND AUTHORITIES REPORTED INDIVIDUAL CASE HISTORIES (Aug 2005 - July 2009)

ADR#	date received dd.mm.yyyy	country	Source	Patient age	patient sex	dose	treatment duration	reaction descriptive	SOC	PT	outcome	Comment/ expectedness/ causality
Serious ADRs												
None												
Non-serious ADRs - Gastrointestinal disorders (n=52)												
[redacted]	19.10.2005	[redacted]	HCP	Ad	NI	tooth brushing	1x/week for 15 years	Nausea for 3 years	Gastrointestinal disorders	Nausea	NI	Possibly related, Listed
[redacted]	06.09.2005	[redacted]	HCP	NI	M	NI	NI	Mouth: Irritation	Gastrointestinal disorders	Stomatitis	NI	Possibly related, Listed
[redacted]	17.11.2005	[redacted]	HCP	NI	M	tooth brushing	1x/week for ca. 10 months	Mouth: Blisters	Gastrointestinal disorders	Oropharyngeal blistering	Recovered after change to alternative fluoride mouth rinse	Possibly related, Listed
[redacted]	16.11.2005	[redacted]	HCP	54	M	tooth brushing	1x/week, 4x	Mouth: Swelling of oral mucosa	Gastrointestinal disorders	Oedema mouth	NI	Possibly related, Listed
[redacted]	13.12.2005	[redacted]	HCP	NI	F	tooth brushing	NI	Mouth: numbness and burning "gingiva problem"	Gastrointestinal disorders	Hypoaesthesia oral, Oral discomfort, Gingival disorder	NI	Possibly related, Listed
[redacted]	13.01.2006	[redacted]	HCP	Ad.	F	NI	NI	Burning of oral mucosa	Gastrointestinal disorders	Oral discomfort	NI	Possibly related, Listed
[redacted]	20.01.2006	[redacted]	HCP	24	F	1.5 cm tooth brushing	once weekly for 3-4min for 4 weeks	Mouth: desquamation of mucosa and numbness	Gastrointestinal disorders	Oral mucosal exfoliation, Hypoaesthesia oral	NI	Possibly related, Listed
[redacted]	29.09.2006	[redacted]	Profession	22	F	normal	2-3min., 1x a week	Oral mucosa, gingiva: burning and swelling of mucosa, white desquamation.	Gastrointestinal disorders	Oral discomfort, Oedema mucosal, Oral mucosal exfoliation, Gingival pain, Gingival swelling	Improved after discontinuation	Possibly related Listed

B

[redacted]	29.12.2006	[redacted]	Profession	NI	NI	normal	once	Swelling of mucosa and tongue	Gastrointestinal disorders	Oedema mucosal, Swollen tongue	NI	Possibly related Listed
[redacted]	11.07.2006	[redacted]	Profession	NI	NI	NI	NI	Desquamation of mucosa	Gastrointestinal disorders	Oral mucosal exfoliation	NI	Possibly related Listed
[redacted]	20.02.2006	[redacted]	Authority	Ad.	F	NI	for long period	Mouth: 1. Swelling 2. Anesthesia of the tongue	Gastrointestinal disorders	Oedema mouth, Hypoaesthesia oral	NI	Possibly related, Listed
[redacted]	22.2.2006	[redacted]	HCP	Ad.	F	normal	2-3 days	Mouth: irritation and swelling of tongue	Gastrointestinal disorders	Stomatitis, Swollen tongue	Recovered	Possibly related, Listed
[redacted]	16.3.2006	[redacted]	HCP	NI	F	normal	2 months, overnight, afterwards 2 min.	Swelling, reddening, burning of gingiva. Allergic reaction suspected.	Gastrointestinal disorders Immune system disorders	Gingival swelling, Gingival erythema, Gingival pain Hypersensitivity	NI	Possibly related (misuse), Listed
[redacted]	16.3.2006	[redacted]	HCP	22	F	normal	once a week for two weeks	inflammation of gingiva	Gastrointestinal disorders	Gingivitis	Recovered.	Possibly related, Listed
[redacted]	20.06.2006	[redacted]	Profession	NI	F	normal	NI	Does not tolerate the taste	Gastrointestinal disorders	Dysgeusia	Improved after discontinuation	Possibly related Listed
[redacted]	04.01.2007	[redacted]	Profession	9	M	normal	days	swelling and burning of mucosa, allergy	Gastrointestinal disorders Immune system disorders	Oedema mouth Oral discomfort Hypersensitivity	allergic reaction confirmed	Related Listed
[redacted]	16.4.2007	[redacted]	Authority BfArM No: 07010123	15	M	NI	NI	Tongue: burning	Gastrointestinal disorders	Glossodynia	NI	Related Listed
[redacted]	30.8.2007	[redacted]	Profession	NI	NI	NI	NI	Tongue: swelling, Gingiva: wounds	Gastrointestinal disorders	Swollen tongue, Gingival disorder	NI	Related Listed
[redacted]	30.10.2007	[redacted]	Profession	65	F	one drop on every root of 4 teeth	once	Gingiva, oral mucosa: strong reddening, swelling, aching, desquamations	Gastrointestinal disorders	Oral discomfort, Oedema mucosal, Oral mucosal exfoliation, Gingival erythema, Gingival swelling, Gingival pain	Improved	Related Listed

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[redacted]	02.11.2007	[redacted]	Profession	34	F	3 x the recommended dose	Once	Burning sensation (mouth), redness, pain, swelling of the tongue, severe inflammation of the oral mucosa; loss of sensation in the tongue	Gastrointestinal disorders, Skin and subcutaneous tissue disorders , General disorders and administration site conditions,	Oral discomfort, Erythema, Pain, Swollen tongue, Stomatitis, Hypoaesthesia oral	Recovered	Related Listed
[redacted]	16.04.2007	[redacted]	Authority BfArM No: 07010123	15	M	NI	NI	Tongue: burning	Gastrointestinal disorders	Glossodynia	NI	Related Listed
[redacted]	13.02.2008	[redacted]	pharmacist	NI	F	NI	NI	Burning sensation in the mouth	Gastrointestinal disorders	Oral discomfort	NI	Related Listed
[redacted]	06.06.2008	[redacted]	pharmacist= consumer	NI	M	recommended by dentist	once	Burning, swelling, redness, irritation of the whole mouth mucosa	Gastrointestinal disorders, Skin and subcutaneous tissue disorders	Oral discomfort, Oedema mouth, Erythema, Stomatitis	Withdrawn	Related Listed
[redacted]	11.06.2008	[redacted]	dentist	80	F	applied by dentist	once	swelling, reddening, ampula format	Gastrointestinal disorders, Skin and subcutaneous tissue disorders	Oedema mouth, Erythema	Withdrawn	Related Listed
[redacted]	02.07.2008	[redacted]	Dentist	NI	F	Normal in the praxis	Only in the praxis	Oral mucosa: burning	Gastrointestinal disorders	Oral discomfort	Withdrawn	Related Listed
[redacted]	29.07.2008	[redacted]	dentist	13	F	NI	after every use	Nausea	Gastrointestinal disorders	Nausea	Withdrawn	Related Listed
[redacted]	22.8.2008	[redacted]	pharmacist	NI	F	normal	overnight	Strong, aching exfoliation of the oral mucosa	Gastrointestinal disorders	Oral mucosal exfoliation	Not withdrawn, got better	Related Listed
[redacted]	10.9.2008	[redacted]	pharmacist	45	F	NI	NI	Wound and pimples in mouth	Gastrointestinal disorders	Mouth injury, Stomatitis	NI	Related Listed
[redacted]	03.10.2008	[redacted]	dentist	NI	F	NI	once	Swelling, reddening and burning of tongue and oral mucosa	Gastrointestinal disorders	Swollen tongue, Tongue disorder, Glossodynia, Oral mucosal erythema, Oral discomfort, Oedema mouth	Withdrawn, recovered	Related Listed

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[redacted]	05.12.2008	[redacted]	dentist	NI	M	NI	overnight	Corrosion of the mouth	Gastrointestinal disorders	Stomatitis	NI	Related Listed
[redacted]	14.07.2009	[redacted]	Pharmacist	55-64	F	toothbrushing	Since years, not rinsed	Nausea, vomiting	Gastrointestinal disorders	Nausea, Vomiting	Improved	Possibly related Listed
[redacted]	04.02.2009	[redacted]	Pharmacist	14	F	As in PIL	since 2 years, with less than once a week	burning sensation after use on tongue, gums, oral mucosa	Gastrointestinal disorders	Glossodynia, Gingival pain, Oral discomfort	Recovered after withdrawal	Possibly related Listed
[redacted]	20.03.2009	[redacted]	Dental practice	23	F	normally	Since many years	Swelling of oral mucosa, nausea, blisters	Gastrointestinal disorders	Oedema mouth, Nausea, Stomatitis	NI	Possibly related Listed
[redacted]	13-01-09	[redacted]	Pharmacist	NI	F	NI	NI	Nausea	Gastrointestinal disorders	Nausea	NI	Possibly related Listed
[redacted]	20.02.2009	[redacted]	Dentist	Sr	F	As written in PIL	Used the product for many years without problem	Exfoliation of upper epithelial layer, oral mucosa reddening, burning, aching, erosions, irritations(happened in May 2008)	Gastrointestinal disorders	Oral mucosal exfoliation, Oral discomfort, Stomatitis, Mouth ulceration, Oral pain, Oral mucosal erythema	Recovered after withdrawal	Possibly related Listed
[redacted]	25.08.2005	[redacted]	HCP	NI	NI	tooth brushing	3-4 years	Teeth: White spots	Gastrointestinal disorders	Tooth discolouration	NI	Possibly related, Unlisted
[redacted]	25.08.2005	[redacted]	HCP	14	NI	tooth brushing	3-4 years	Teeth: White spots	Gastrointestinal disorders	Tooth discolouration	NI	Possibly related, Unlisted
[redacted]	25.08.2005	[redacted]	HCP	17	M	tooth brushing	3-4 years	Teeth: Discoloration	Gastrointestinal disorders	Tooth discolouration	NI	Possibly related, Unlisted
[redacted]	17.11.2005	[redacted]	HCP	NI	NI	NI	NI	Teeth: Yellowish discoloration	Gastrointestinal disorders	Tooth discolouration	NI	Possibly related, Unlisted
[redacted]	13.02.2006	[redacted]	HCP	NI	F	once a week	2 min.	Pain at teeth and gingiva	Gastrointestinal disorders	Toothache, Gingival pain	Treatment with Paracetamol 500mg	Possibly related, Unlisted
[redacted]	23.1.2006	[redacted]	HCP	Ad.	M	NI	first time	Gingiva: reddening, bleeding and burning	Gastrointestinal disorders	Gingival erythema, Gingival bleeding, Gingival pain	NI	Possibly related, Unlisted

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[redacted]	24.07.2006	[redacted]	Profession	NI	NI	NI	NI	Discoloration (mouth)	Gastrointestinal disorders	Mouth discolouration	NI	Possibly related Unlisted
[redacted]	29.09.2006	[redacted]	Profession	40	M	normal	NI	White spots on teeth	Gastrointestinal disorders	Tooth discolouration	Improved after discontinuation	Possibly related Unlisted
[redacted]	09.03.2007	[redacted]	Profession	NI	NI	loaded tray	2x 2.5 min.	Discoloration of teeth	Gastrointestinal disorders	Tooth discolouration	NI	Unlikely related Unlisted
[redacted]	05.04.2007	[redacted]	Profession	NI	NI	NI	NI	Teeth: light-colored spots	Gastrointestinal disorders	Tooth discolouration	NI	Unlikely related Unlisted
[redacted]	13.07.2007	[redacted]	Profession	NI	NI	NI	NI	Gingiva, Tongue: thick, reddening, numbness, difficulties in breathing	Gastrointestinal disorders, Respiratory, thoracic and mediastinal disorders	Tongue disorder, Hypoaesthesia oral, Dyspnoea. Gingival erythema	NI	Possibly related Unlisted
[redacted]	18.10.2007	[redacted]	Profession	NI	NI	NI	NI	Gingiva, tongue: white discoloration	Gastrointestinal disorders	Tongue discolouration, Gingival discolouration	NI	Possibly related Unlisted
[redacted]	23.10.2008	[redacted]	dentist	63	M	NI	NI	burning of oesophagus Coughing, after swallowing	Gastrointestinal disorders Respiratory, thoracic and mediastinal disorders	Oesophageal pain Cough	AR lasted a couple of days	Related Unlisted
[redacted]	22.01.2009	[redacted]	Pharmacist	29	F	With dental tray	Left 15 minutes without rinsing (misuse)	Oral mucosa: pain, swelling,reddening, desquamation blisters, aphthae, taste lost cracks on tongue	Gastrointestinal disorders, Nervous system disorders, Injury, poisoning and procedural complications	Oral discomfort, Oedema mouth, Oral mucosal exfoliation, Oropharyngeal blistering, Aphthous stomatits Ageusia, Tongue injury	Withdrawn, resolved	Possibly related Unlisted
[redacted]	10.03.2009	[redacted]	Dentist	48	F	Daily use (spoon amount)	5 min daily with a dental bar	Nausea, Vomiting, Diarrhea, Headache, Stomach ache, Blisters in mouth	Gastrointestinal disorders Nervous system disorders	Nausea, Vomiting, Diarrhoea, Abdominal pain upper Stomatitis, Headache	Unchanged after product withdrawal	Possibly related Unlisted

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[redacted]	26.06.2009	[redacted]	Dentist	Ad.	F	toothbrus hing	2 min and rinsing	Swelling of the upper jaw, reddening of gums in the underjaws, whitish oral mucosa	Gastrointestinal disorders	Gingival swelling, Gingival erythema, Oral mucosal discolouration	NI	Possibly related Unlisted
[redacted]	16.01.2009	[redacted]	Dentist	6	F	NI	NI	White stains (calcareous)	Gastrointestinal disorders	Mucosal discolouration	NI	Possibly related Unlisted
Non-serious ADRs : Skin and subcutaneous tissue disorders (n=3)												
[redacted]	18.11.2005	[redacted]	HCP	NI	M	NI	NI	Contact eczema	Skin and subcutaneous tissue disorders	Dermatitis contact	Patch test positive to Elmex Gelee	Related, Unlisted
[redacted]	30.01.2006	[redacted]	HCP	Ad.	F	NI	NI	Burning and swelling of face	Skin and subcutaneous tissue disorders Nervous system disorders	Swelling face Burning sensation	NI	Possibly related, Unlisted
[redacted]	22.01.2009	[redacted]	dermatologis t	61	M	As in the PIL	once	Generalised urticaria, acute swelling on face and in oral mucosa	Skin and subcutaneous tissue disorders , General disorders and administration site conditions, Gastrointestinal disorders	Urticaria, Face oedema, Oedema mouth	Withdrawn, resolved after cortisone injection, positive patch test to sodium fluoride	Related Unlisted
Non-serious ADRs : Immune system disorders (n=1)												
[redacted]	13.02.2007	[redacted]	Profession	46	F	normal	2 min.	allergic reaction	Immune system disorders	Hypersensitivity	product set up, got better	Related Listed
Non-serious ADRs : Injury, poisoning and procedural complications (n=2)												
[redacted]	16.01-09	[redacted]	Dentist	NI	M	NI	NI	Discoloration on the prosthesis	Injury, poisoning and procedural complications	Device interaction	NI	Possibly related Unlisted
[redacted]	28.01.2008	[redacted]	pharmacist	NI	M	NI	weeks	Chemical burn around nails of the toe	Injury, poisoning and procedural complications	Chemical burn of skin	off label topical skin for the self medication of mycosal infection	Related Unlisted

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Non-serious ADRs : Nervous system disorders (n = 2)												
[redacted]	10.02.2009	[redacted]	Pharmacist	Ad.	M	overdosed	Applied with a custom made dental mould and not rinsed after 5 minutes	Dizziness , vision blurred (white spots)	Nervous system disorders, Eye disorders	Dizziness, Vision blurred, Visual impairment	NI	Possibly related Unlisted
[redacted]	10.03.2009	[redacted]	Dentist	12	M	3 x / day	1 week	Unconsciousness, possible hypersensitivity reaction	Nervous system disorders, Immune system disorders	Loss of consciousness, Hypersensitivity	Received calcium at the hospital and left after	Possibly related Unlisted
Non-serious ADRs : Musculoskeletal and connective tissue disorders (1)												
[redacted]	28.12.2005	[redacted]	HCP	Ad.	F	NI	NI	Muscle pain	Musculoskeletal and connective tissue disorders	Myalgia	NI	Possibly related, Unlisted

NI = Non Indicated
Ad = Adult

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APPENDIX 5
PRESENTATION OF CONSUMER REPORTED OR UNRELATED INDIVIDUAL CASE HISTORIES (June 2006 - May 2009)

ADR #	date received dd.mm.yyyy	country	Source	Patient age	patient sex	dose	treatment-duration	reaction descriptive	SOC	PT	outcome	Comment/ expectedness/ causality
Serious ADRs												
None												
Non-serious ADRs: Gastrointestinal disorders (49)												
[redacted]	15.09.2005	[redacted]	Consumer	NI	F	Tooth brushing	since 20 years	Mouth: desquamation of oral mucosa	Gastrointestinal disorders	Oral mucosal exfoliation	NI	Possibly related, Listed
[redacted]	25.08.2005	[redacted]	Consumer	NI	M	NI	NI	Nausea	Gastrointestinal disorders	Nausea	NI	Possibly related, Listed
[redacted]	27.09.2005	[redacted]	Consumer	64	F	tooth brushing	every second day, for 10 weeks	Mouth: pain and burning of oral mucosa; reddening of gingiva	Gastrointestinal disorders	Oral pain, Oral discomfort, Gingival erythema	NI	Possibly related, Listed
[redacted]	11.10.2005	[redacted]	Consumer	Ad.	F	tooth brushing	once	Mouth: Burning and desquamation	Gastrointestinal disorders	Oral discomfort, Oral mucosal exfoliation	Recovered	Possibly related, Listed
[redacted]	07.10.2005	[redacted]	Consumer	NI	M	NI	NI	Vomiting	Gastrointestinal disorders	Vomiting	NI	Possibly related, Listed
[redacted]	07.011.2005	[redacted]	Consumer	66	F	tooth brushing	for years	Mouth: Irritation	Gastrointestinal disorders	Stomatitis	Recovered after rinsing with water	Possibly related, Listed
[redacted]	22.12.2005	[redacted]	Consumer	Ad.	M	tooth brushing	NI	Nausea	Gastrointestinal disorders	Nausea	NI	Possibly related, Listed
[redacted]	10.4.2006	[redacted]	Consumer	62	M	normal	5 min. without rinsing , afterwards tray applicatio n	Inflammation of oral mucosa	Gastrointestinal disorders	Stomatitis	NI	Possibly related, Listed
[redacted]	19.04.2006	[redacted]	Consumer	NI	M	NI	1h tray applicatio n	Burning of tongue	Gastrointestinal disorders	Glossodynia	NI	Possibly related, Listed

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[redacted]	26.09.2006	[redacted]	Consumer	46	F	normal	2-3 months	desquamation and irritation of mucosa	Gastrointestinal disorders	Oral mucosal exfoliation, Stomatitis, Hypoaesthesia oral	NI	Possibly related Listed
[redacted]	07.02.2007	[redacted]	Consumer	6	M	Normal	2x daily	Lips, mouth: irritation reddening	Gastrointestinal disorders	Cheilitis, Stomatitis	NI	Related Listed
[redacted]	14.02.2007	[redacted]	Consumer	33	F	Normal	1xweek	Entire oral mucosa: blisters, aphthae	Gastrointestinal disorders	Oropharyngeal blistering, Aphthous stomatitis	NI	Related Listed
[redacted]	20.02.2007	[redacted]	Consumer	NI	NI	NI	NI	Oral mucosa: desquamations	Gastrointestinal disorders	Oral mucosal exfoliation	NI	Related Listed
[redacted]	27.02.2007	[redacted]	Consumer	NI	M	Normal	Once	Irritation and numbness of oral mucosa	Gastrointestinal disorders	Stomatitis, Hypoaesthesia oral	Improved	Related Listed
[redacted]	21.11.2007	[redacted]	Customer	NI	M	as recommended	3 times	Aphthae in the mouth affecting the whole mouth mucosa	Gastrointestinal disorders	Aphthous stomatitis	Recovered	Related Listed
[redacted]	17.12.2007	[redacted]	Customer	NI	F	as recommended	20 years	Burning, swelling, pain in the whole mouth affecting lips as well	Gastrointestinal disorders	Oral discomfort, Oedema mouth Oral pain, Cheilitis	Withdrawn	Related Listed
[redacted]	05.03.2008	[redacted]	consumer	NI	F	recommended	years	swelling of lips and whole oral mucosa	Gastrointestinal disorders	Lip swelling, Oedema mouth,	Withdrawn	Related Listed
[redacted]	17.04.2008	[redacted]	consumer	NI	M	as recommended by the dentist	once daily for four days	Scaling off the gum and mouth mucosa	Gastrointestinal disorders	Oral mucosal exfoliation	NI	Related Listed
[redacted]	06.06.2008	[redacted]	consumer	NI	F	as recommended	1xweekly/ every other week	Burning, swelling, redness, irritation of the gums	Gastrointestinal disorders	Oral discomfort, Oedema mouth, Stomatitis	Recommendation to stop the product and use camomilla tea.	Related Listed
[redacted]	29.05.2008	[redacted]	Consumer	NI	M	As recommended by the dentist	Once	Swelling and numbness of the tongue and gums	Gastrointestinal disorders	Swollen tongue Hypoaesthesia oral, Gingival swelling	NI	Related Listed
[redacted]	02.09.2008	[redacted]	consumer	39	NI	application the teeth at home	7 or 10 minutes	Desquamation, inflammation of the oral mucosa, burning of mouth	Gastrointestinal disorders	Oral mucosal exfoliation, Oral discomfort	Withdrawn	Related Listed

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[redacted]	28.07.2009	[redacted]	Consumer	Ad.	F	4-5 times In a mold	30 min	Gums and cheek exfoliation, tongue exfoliation, lip exfoliation	Gastrointestinal disorders	Oral mucosal exfoliation, Tongue exfoliation, Lip exfoliation	Not recovered after 24 hours	Possibly related, Listed Other medic: Alendron beta (osteoporosis), anti-hormone therapy (cancer)
[redacted]	08.07.2009	[redacted]	Consumer	35-44	F	Normal use with rinsing	Since years	Burning sensation on tongue in the night	Gastrointestinal disorders	Glossodynia	Improving but not fully recovered 24 hours later	Possibly related, Listed
[redacted]	10.10.2006	[redacted]	Consumer	NI	F	NI	NI	desquamation of mucosa after too long treatment in tray	Gastrointestinal disorders, Psychiatric disorders	Oral mucosal exfoliation, Intentional drug misuse	NI	Possibly related Unlisted
[redacted]	03.10.2006	[redacted]	Consumer	67	F	normal	4 times in 4 weeks	Desquamation of mucosa, blisters, pain and white tongue layer	Gastrointestinal disorders	Oral mucosal exfoliation, Oral discomfort, Oropharyngeal blistering, Coated tongue	NI	Possibly related Unlisted
[redacted]	24.11.2006	[redacted]	Consumer	45	F	normal	10 years	burning, pain, numbness of tongue	Gastrointestinal disorders	Oral discomfort, Oral pain Hypoaesthesia oral	NI	Possibly related Unlisted
[redacted]	02.08.2007	[redacted]	Consumer	NI	F	normal	1x week (2 weeks)	Upper lips:swelling	Gastrointestinal disorders	Lips swelling	product set up, got better	Related Unlisted
[redacted]	04.05.2007	[redacted]	Consumer	NI	NI	NI	NI	Sore throat	Gastrointestinal disorders	Oropharyngeal pain	NI	Related Unlisted
[redacted]	25.06.2007	[redacted]	Consumer	NI	NI	NI	NI	Tongue: prickling	Gastrointestinal disorders	Hypoaesthesia oral	NI	Possibly related Unlisted
[redacted]	15.07.2007	[redacted]	Consumer	NI	NI	NI	NI	Teeth: gritting	Gastrointestinal disorders	Bruxism	NI	Unlikely related Unlisted
[redacted]	10.08. 2007	[redacted]	Consumer	NI	NI	NI	NI	Tongue: brown discoloration	Gastrointestinal disorders	Tongue discolouration	NI	Unlikely related Unlisted
[redacted]	12.09.2007	[redacted]	Consumer	9	F	normal	since half year	Lips, face: oedema swelling, skin rash, body: itching	Gastrointestinal disorders, Skin and subcutaneous tissue disorders	Lip swelling, Swelling face, Rash, Pruritus	product set up, got better	Related Unlisted

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[redacted]	20.09.2007	[redacted]	Consumer	42	F	very much amounts	after every teeh prophylax y session	Tongue, oral mucosa: burning, erosions	Gastrointestinal disorders, Injury, poisoning and procedural complications	Glossodynia, Oral discomfort, Tongue injury, Stomatitis and ulceration	product set up, got better,allergic test will be done	Possibly related Unlisted
[redacted]	23.10.2007	[redacted]	Consumer	NI	F	NI	NI	many aphtens in mouth and throat reddening	Gastrointestinal disorders	Aphthous stomatitis Pharyngeal erythema	NI	Possibly related Unlisted
[redacted]	09.03.2009	[redacted]	Consumer	NI	F	NI	NI	Lips visibly swelled +face	Gastrointestinal disorders	Lip swelling, Swelling face	NI	Possibly related Unlisted
[redacted]	22.01.2009	[redacted]	Consumer	NI	NI	In excess on gum, mucosa, all over the mouth	NI	Mouth irritation, pain	Gastrointestinal disorders	Stomatitis, Oral pain	NI	Possibly related Unlisted
[redacted]	09.01.2009	[redacted]	Consumer	NI	F	NI	regularly	Swelling of the lips and face	Gastrointestinal disorders	Lip swelling, Swelling face,	NI	Possibly related Unlisted
[redacted]	18.02.2009	[redacted]	Doctor	Ad.	NI	In excess	2-3 min	Furry tongue (numb), the next day voice was croaking, enunciation problems	Gastrointestinal disorders, Respiratory, thoracic and mediastinal disorders, Nervous system disorders	Tongue coated, Hypoaesthesia oral, Dysphonia, Dysarthria	NI	Non related (denied by HCP) Unlisted
[redacted]	12.02.2009	[redacted]	Consumer	Ad.	F	Large amount (excessive)	6-7 minutes without rinsing	Gum lesions	Gastrointestinal disorders	Gingival disorder	Recovered after withdrawn	Possibly related Unlisted
[redacted]	02.08.2007	[redacted]	Consumer	NI	F	normal	1x week (2 weeks)	Upper lips:swelling	Gastrointestinal disorders	Lip swelling	Product set up, got better	Related Unlisted
[redacted]	29.09.2005	[redacted]	Consumer	44	F	Normal dose, 2 x / day	10 min each time	Mouth: burning and swelling of gingival and lips	Gastrointestinal disorders Nervous system disorders	Gingival pain, Gingival swelling, Lip swelling, Burning sensation	Misuse. Reduction of time to 5 minutes lead to no reaction.	Likely related, Unlisted
[redacted]	20.03.2006	[redacted]	Consumer	37	M	Fully filled tray applicatio n	overnight	Gingival : Whitening and Erosion	Gastrointestinal disorders	Gingival discolouration, Gingival erosion	Misuse. Discoloration recovered, erosion persisted longer.	Likely related, Unlisted
[redacted]	20.10.2005	[redacted]	Consumer	20-30	F	tooth brushing	1x/week	Teeth: White spots	Gastrointestinal disorders	Tooth discolouration	Recovered	Possibly related, Unlisted

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[redacted]	19.10.2005	[redacted]	Consumer	NI	NI	NI	3 weeks (3x)	Teeth: Discoloration	Gastrointestinal disorders	Tooth discolouration	NI	Possibly related, Unlisted
[redacted]	1.11.2005	[redacted]	Consumer	NI	F	tooth brushing	for years	Mouth: Blisters on tongue and throat	Gastrointestinal disorders Respiratory, thoracic and mediastinal disorders	Tongue blistering, Oropharyngeal blistering	NI	Possibly related, Unlisted
[redacted]	15.05.2006	[redacted]	Consumer	68	M	normal	NI	nausea, vomiting, diarrhoea, shivering	Gastrointestinal disorders General disorders and administration site conditions,	Nausea, Vomiting, Diarrhoea Chills	NI	Possibly related, Unlisted
[redacted]	05.07.2009	[redacted]	Consumer	Sr	F	NI	Kept in mouth overnight	Gum bleeding and sensitive when brushing teeth in the next morning	Gastrointestinal disorders	Gingival pain, Gingival bleeding	Recovered over the day	Possibly related, Unlisted
[redacted]	24.07.2009	[redacted]	Consumer	child	F	In office treatment	NI	Felt bad 2 days later	General disorders and administration site conditions	Feeling abnormal	NI	Possibly related, Unlisted Child allergic to Gluten
[redacted]	23.01.2009	[redacted]	consumer	Ad.	F	NI	NI	Nausea	Gastrointestinal disorders	Nausea	Withdrawn	Possibly related Unlisted
Non-serious ADRs : Skin and subcutaneous tissue disorders (2)												
[redacted]	11.10.2006	[redacted]	Consumer	9	M	normal	once	swelling of sides of the face	Skin and subcutaneous tissue disorders	Swelling face	NI	Possibly related Listed
[redacted]	30.04.2007	[redacted]	Consumer	NI	NI	NI	NI	Face and oral mucosa: Rash, spots	Skin and subcutaneous tissue disorders, Gastrointestinal disorders	Rash, Stomatitis	NI	Related Unlisted
Non-serious ADRs : Respiratory, thoracic and mediastinal disorders (1)												
[redacted]	04.05.2007	[redacted]	Consumer	NI	NI	NI	NI	Sore throat	Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	NI	Related Unlisted
Non-serious ADRs : General disorders and application site condition (1)												
[redacted]	19.09.2007	[redacted]	Consumer	40	M	normal	since 15 years	Problems to fall asleep	Nervous system disorders	Initial insomnia	Product set up, got better	Related Unlisted

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Non-serious ADRs : Injury, poisoning and procedural complications (1)												
[redacted]	18.09.2007	[redacted]	Consumer	11 months	M	NI	NI	ate elmex gelee, no reactions no AR	Injury, poisoning and procedural complications	Accidental exposure	NI	No AR
Non-serious ADRs : Immune system disorders (2)												
[redacted]	07.06.2006	[redacted]	Consumer	NI	F	Normal dose	Since years	Allergic reaction (face swelling, swelling of oral mucosa, pharynx and nasal cavity)	Immune system disorders, Oropharyngeal swelling	Hypersensitivity, Swelling face, Oropharyngeal swelling	Recovered	Related Listed
[redacted]	07.06.2006	[redacted]	Consumer	NI	F	Normal dose	Since years	Allergic reaction : face swelling, swelling of oral mucosa, pharynx and nasal cavity	Immune system disorders Skin and subcutaneous tissue disorders, Respiratory, thoracic and mediastinal disorders	Hypersensitivity Swelling face Oropharyngeal swelling, Nasal congestion	Recovered	Likely related, Unlisted
Non-serious ADRs : Nervous system disorders (1)												
[redacted]	13.02.2006	[redacted]	Consumer	Ad.	M	1 cm toothbrushing	once weekly, 5-6 min.	Change to salty taste for weeks	Nervous system disorders	Dysgeusia	NI	Possibly related, Listed

NI = Non Indicated
Ad = Adult

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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, issued from the line listing of medically confirmed/authorities reported cases (cumulative since launch for serious unlisted)

Terms (SOC & PT)	Serious cases		Non-serious cases		Total
	unlisted terms*	listed terms	unlisted terms	listed terms	
• **Gastro-intestinal disorders**	**0**	**0**	**17**	**91**	**108**
Oral discomfort	-	-	-	13	13
Oral pain	-	-	-	1	1
Hypoaesthesia oral	-	-	-	5	5
Oedema mouth	-	-	-	9	9
Oedema mucosal,	-	-	-	3	3
Oral mucosal exfoliation,	-	-	-	7	7
Oral mucosal erythema,	-	-	-	2	2
Gingival erythema,	-	-	-	5	5
Gingival disorder	-	-	-	2	2
Gingival swelling,	-	-	-	4	4
Gingival pain	-	-	-	6	6
Gingival bleeding	-	-	1	-	1
Stomatitis	-	-	-	8	8
Mouth ulceration	-	-	-	1	1
Aphthous stomatits	-	-	-	1	1
Mouth injury	-	-	-	1	1
Tongue disorder,	-	-	-	2	2
Swollen tongue	-	-	-	5	5
Glossodynia	-	-	-	4	4
Oesophageal pain	-	-	1	-	1
Oropharyngeal blistering,	-	-	-	2	2
Dysgeusia	-	-	-	1	1
Nausea	-	-	-	6	6
Vomiting,	-	-	-	2	2
Diarrhoea,	-	-	1	-	1
Abdominal pain upper	-	-	1	-	1
Mucosal discolouration	-	-	1	-	1
Gingival discolouration	-	-	1	-	1
Mouth discolouration	-	-	1	-	1
Tongue discolouration,	-	-	1	-	1
Tooth discolouration	-	-	7	-	7
Oral mucosal discolouration	-	-	1	-	1
Gingivitis	-	-	-	1	1
Toothache	-	-	1	-	1

• **General disorders and administration site conditions**	0	**0**	**0**	**2**	**2**
Pain	-	-	-	1	1
Face oedema	-	-	-	1	1
• **Immune system disorders**	**0**	**0**	**0**	**4**	**4**
Hypersensitivity	-	-	-	4	4
• **Respiratory, thoracic and mediastinal disorders**	**0**	**0**	**2**	**0**	**2**
Cough	-	-	1	-	1
Dyspnoea	-	-	1	-	1
• **Skin and subcutaneous tissue disorders**	**0**	**0**	**1**	**5**	**6**
Urticaria	-	-	-	1	1
Erythema	-	-	-	3	3
Dermatitis contact	-	-	1	-	1
Swelling face	-	-	-	1	1
• **Nervous system disorders**	**0**	**0**	**4**	**1**	**5**
Dizziness	-	-	1	-	1
Loss of consciousness	-	-	1	-	1
Ageusia	-	-	1	-	1
Headache	-	-	1	-	1
Burning sensation	-	-	-	1	1
• **Injury, poisoning and procedural complications**	**0**	**0**	**3**	**0**	**3**
Tongue injury	-	-	1	-	1
Device interaction	-	-	1	-	1
Chemical burn of skin	-	-	1	-	1
• **Eye disorders**	**0**	**0**	**2**	**0**	**2**
Vision blurred	-	-	1	-	1
Visual impairment	-	-	1	-	1
• **Musculoskeletal and connective tissue disorders**	**0**	**0**	**1**	**0**	**1**
Myalgia	-	-	1	-	1
TOTAL	**0**	**0**	**30**	**103**	**133**

There were **no Serious Unlisted ADRs** before the period of this PSUR

All Terms are issued from 61 case reports (from line listing appendix 4) : 36 listed + 25 unlisted (with at least 1 term being unlisted)

APPENDIX 7

LITERATURE REFERENCES FOR SODIUM FLUORIDE

- **1. 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.

- **2. 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.

- **3) Reddy PS, Pushpalatha T, Reddy PS.**
  Suppression of male reproduction in rats after exposure to sodium fluoride during early stages of development.
  Naturwissenschaften. 2007 Jul;94(7):607-11.

  Summary
  Sodium fluoride (NaF), a widespread natural pollutant was given to sperm-positive female rats throughout gestation and lactation at a dose of 4.5 and 9.0 ppm via drinking water. The neonates were allowed to grow up to 90 days on tap water, and then sperm parameters, testicular steroidogenic marker enzyme activity levels, and circulatory hormone levels were studied. The sperm count, sperm motility, sperm coiling (hypoosmotic swelling test), and sperm viability were decreased in experimental rats when compared with controls. The activity levels of testicular steroidogenic marker enzymes (3beta hydroxysteroid dehydrogenase and 17beta hydroxysteroid dehydrogenase) were significantly decreased in experimental animals indicating decreased steroidogenesis. The serum testosterone, follicle stimulating hormone and luteinizing hormone levels were also significantly altered in experimental animals. Our data indicate that exposure to NaF during gestation and lactation affects male reproduction in adult rats by decreasing spermatogenesis and steroidogenesis.

- **4) 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.

- **5) 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.