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NOVARTIS

Drug Safety and Pharmacovigilance (DSP)

Zymafluor® (sodium fluoride)

PERIODIC SAFETY UPDATE REPORT 4 (PSUR 4)

Period covered by this report: 01 Apr 2006 – 31 Jan 2009

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Executive PSUR summary

This document is the Fourth PSUR for Zymafluor® (sodium fluoride) covering the time period from 01 Apr 2006 to 31 Jan 2009.

The product is now approved in more than 34 countries for the prevention of dental caries (see Appendix 2 for an overview of the registration status). The current Core Data Sheet (CDS) is the Summary of Product Characteristics (SPC) dated 05 Dec 2006. During the review period, the SPC was updated with a reduction of shelf-life from 48 to 36 months and a change in storage conditions for Zymafluor® 0.25 mg tablets.

No patients received Zymafluor® in Novartis sponsored clinical trials. On the basis of sales data, the patient exposure was estimated as approximately 1.4 million patient-years.

A total of 55 spontaneous case reports were received during the review period, 3 of which were regarded as serious (3 unlisted), and 52 as non-serious (19 unlisted). There were no serious suspected solicited reports. Cumulatively, the safety database contains 325 spontaneous reports, including 10 serious unlisted reports.

No important targeted safety studies were identified.

In the previous PSUR, three events (in a single case) namely loss of consciousness, dyspnea, and cyanosis have been identified as relevant safety findings. During the review period, no new cases were received and the available cumulative data does not suggest a causal relationship with the product. Therefore loss of consciousness, dyspnea and cyanosis are no longer considered relevant safety findings.

No new relevant safety findings were identified. The safety data remains in accordance with the previous cumulative experience and the safety information presented in the SPC.

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List of abbreviations

CDS	Core Data Sheet
CMC	Chemistry, Manufacturing and Controls
CSI	Core Safety Information
DDD	Defined Daily Dose
DSP	Drug Safety and Pharmacovigilance
EU	European Union
HCP	Health Care Professional

HLGT	High Level Group Term
HLT	High Level Term (of MedDRA)
IBD	International Birth Date
ICH	International Conference on Harmonization
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PMS	Post marketing surveillance
PSUR	Periodic Safety Update Report
PT	Preferred Term (of MedDRA)
SPC	Summary of Product Characteristics
SOC	System Organ Class (of MedDRA)

1 Introduction

This document is the fourth Periodic Safety Update Report (PSUR 4) on Zymafluor® (active ingredient: sodium fluoride) compiled for regulatory authorities in the format detailed in the ICH E2C and EU guidelines (ICH E2C, 1996; Addendum to ICH E2C, 2003; EU Volume 9A; 2008). It summarizes the safety data received and processed by Drug Safety and Pharmacovigilance (DSP) of Novartis Consumer Health from worldwide sources for the period covering 01 Apr 2006 until 31 Jan 2009. The periodicity of this PSUR was modified in order to synchronize NCH PSUR periodicity to the EU Harmonized Data-Lock Point of sodium fluoride (additional list of EU HBDs and DLPs, alphabetical order, dated 15 Jul 2008 posted on the HMA website). The current report is complementary to the previous PSUR, PSUR 3, covering the period from 01 Apr 2001 until 31 Mar 2006 (Bonavitacola, 2006). The next Zymafluor® PSUR will cover the period from 01 Feb 2009 until 31 Jan 2012. The product is referred to as Zymafluor in the remainder of the document.

A formulation containing sodium fluoride (0.25 mg tablets) combined with 500 or 1000 I.U. of vitamin D is available under the trademark Zymafluor-D®. Safety data concerning this product is presented in a PSUR covering the period from 01 Jan 2002 to 31 Dec 2006. A relevant safety finding, namely "hypercalcaemia" at therapeutic doses, was identified during the review period of this Zymafluor-D® PSUR. However, Vitamin D is the most likely of all vitamins to cause hypercalcaemia in case of overdosage.

Fluoride toothpaste/gel and mouth rinse solution are also available under the trademark Zymafluor® but they are not included in this PSUR because they contain much lower doses of fluoride and are not registered as medicines but as "oral hygiene" products. Therefore, no PSUR are required.

Further details on mechanism of action, indications, pharmaceutical forms and instructions for use are presented in the Core Data Sheet (Appendix 1).

2 Worldwide marketing authorization status

Zymafluor was first registered in Switzerland on 16 June 1950 (International Birth Date). It is currently approved in more than 34 countries worldwide including 16 in Europe. For a complete overview of the registration status, reference is made to Appendix 2.

3 Update of Regulatory Authority or MAH actions taken for safety reasons

During the period covered by this report, there was no marketing authorization withdrawal or suspension, no failure to obtain a marketing authorization renewal, no restrictions on distribution and no clinical trial suspension.

4 Changes to reference safety information

4.1 Amendments to Core Safety Information

The CDS in effect at the beginning of the period covered is the SPC dated 14 Apr 2003.

During the review period of this report, the core safety information (CSI) was amended following a Chemistry, Manufacturing and Controls (CMC) Type II Variation for reduction of shelf-life from 48 to 36 months and a change in storage conditions for Zymafluor 0.25 mg tablets (variation dispatched to countries in Nov 2006). These changes were not related to safety. The revised SPC, currently in use, is dated 05 Dec 2006 and is enclosed in Appendix 1.

4.2 Amendments to country prescribing information

Amendments to the safety information of the prescribing information made during the review period in countries where the product is registered which constituted a meaningful difference with the core safety information are listed below (additions in *italics* and deletions in *strikethrough*).

Belgium, the Netherlands

The following information was added:

Section 4.1 "Therapeutic indications":

In the Netherlands:
Prevention *and reduction* of dental caries

Section 4.2 "Posology and method of administration"

In the Netherlands:

0-2 yr: 1 tablet/day
2-5 yr: 2x1 tablet/day
5-12 yr: if advised by dentist: continue with 2x1 tablet/day.
- Tablets to be taken spread out over the day.
- Not immediately before or after brushing teeth.
- Only one tablet at a time
- Not on an empty stomach

In Belgium:

0-2 yr: 1 tablet/day
2-14 yr: 2x1 tablet/day
-Do not swallow
-Best just before bedtime

Section 4.4. "Special warnings and special precautions for use", in the Netherlands:

- 0,5-1 mg in a short period (30 min) during several weeks or months can result in visible enamel fluorose (mottled enamel)

- use only after medical advice in case of kidney insufficiency.

Section 4.5. "Interactions with other medicaments and other forms of interaction", in the Netherlands:

The absorption of fluoride is related to the solubility of the compound ingested, absorption is inhibited by calcium, magnesium or aluminium *or iron.* Zymafluor® should therefore not be given with milk and dairy products nor with antacids containing calcium, aluminium or magnesium salts.

Section 4.6. "Pregnancy and lactation", in Belgium:

A beneficial effect on the baby by using fluorides during pregnancy has NOT been established.

Section 4.8 "Undesirable effects", in Belgium:

- prolonged use can result in enamel fluorose

- long-term and excessive use can lead to bone fluorose.

Hungary:

Meaningful changes between the Hungarian text and the Core SPC:

In section 4.3. "Contra-indications":
Hypersensitivity to any of the constituents, *considerable renal impairment or when the fluoride content of the drinking water is more than 0,7 mg/l.*

In section 4.4. "Special warnings and special precautions for use":
When considering fluoride supplementation, allowance should be made for fluorides ingested from other sources so as to avoid overdosage.
In areas where table salt or water is fluoridated, the dosage of Zymafluor should be reduced.
If the water contains more than 0,7 mg/l of fluoride, supplementation is not recommended.

If the child regularly gets fluoride content tablet (e.g. Dentocar) in kindergarten or in school, Zymafluor may be applied only at weekends and on holydays.

In section 4.8. "Undesirable effects":
~~*At the doses recommended for caries prophylaxis, fluoride has not been shown to have significant side-effects.*~~ However rare cases of mild skin rashes (erythema, urticaria) have been reported. They disappear rapidly on stopping treatment.

In section 4.9. "Overdose":

[...]
The lethal dose in adults (70 kg) is stated to be between 2,2 g - 4,5 g fluoride,. In 10 kg children approx. 200 mg fluoride may be fatal.

i.e. approximately ~~*900*~~ *800* Zymafluor ¼ mg tablets.

[...]

Germany (*local formula*)

Meaningful changes between the German text and the Core SPC identified during the review period:

In section 4.3. "Contra-indications":
[...]
Additionally for Zymafluor 0.5 mg and Zymafluor 1.0 mg:
Due to its content of peppermint oil Zymafluor 0.5 mg and Zymafluor 1.0 mg must not be used in patients with bronchial asthma or other respiratory tract disorders, which come along with distinctive intolerance of the respiratory tract. The inhalation of Zymafluor 0.5 mg and Zymafluor 1.0 mg respectively, may result in bronchoconstriction.

In section 4.4. "Special warnings and special precautions for use":
[...]
If the content of fluoride of the water (drinking water or mineral water) used for the feeding of the baby or infant is higher than 0.3 mg per liter, the intake of fluoride in the first 3 years of age is not necessary. (For children which are exclusively breastfed this limitation is not valid).
Children under the age of 3 years should not use fluoride containing toothpaste in case of systemic fluoride intake.
In case of severe chronic disorders which affect growth, the fluoride prophylaxis should be decided in each individual case.

In section 4.6. "Pregnancy and lactation":
The intake of fluoride during pregnancy is not contraindicated but probably without benefit for the denture of the child.
[...]

In section 4.8. "Undesirable effects":
Adverse reactions are ranked under heading of frequency , the most frequent first, using the following convention:
- *very common (≥1/10)*
- *common (≥1/100 to <1/10)*
- *uncommon (≥1/1000 to <1/100)*
- *rare (≥1/10000 to <1/1000)*
- *very rare (<1/10000)*
- *not known (frequency not assessable based on the available data)*[...]

5 Patient exposure

5.1 Investigational clinical trials

No patients received Zymafluor treatment in Novartis-sponsored investigational clinical trials or in Post-Marketing Surveillance (PMS) studies during the review period.

5.2 Market experience

The number of patients treated with Zymafluor during the review period is difficult to estimate as the daily dosage and the duration of treatment may need to be adapted according to the age of the child, the fluoride content of drinking water and the fluorides ingested from other sources such as from diet and fluoride toothpaste.

An estimate of patient exposure is calculated based on [redacted]

A

In the previous PSUR period covering 01 Apr 2001 until 31 Mar 2006, the estimated patient exposure was 5'005'655 patient-years.

The cumulative patient exposure since the first PSUR (01 Apr 1991) is estimated to be approximately 16'652'808 patient-years.

6 Presentation of individual case histories

6.1 Definitions and presentation of cases in line listings and summary tabulations

Definitions

A **serious** event is one that results in death, is life-threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization or prolongation of existing hospitalization, or is a congenital anomaly/birth defect. In addition, other situations are also usually considered serious such as important medical events which may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

An **unlisted** event is one whose nature, severity, specificity or outcome is not consistent with the information included in the SPC.

Listedness of events is determined at the time of receipt of the report. The events related to a leading diagnosis will receive the same assessment as the leading event.

Line listings

All spontaneous, unpublished and published individual reports, as well as reports derived from clinical trials meeting the criteria defined below, are presented in line listings in Appendix 3 of the PSUR.

Reports are included in the appropriate line listings according to case level assessments. Line listings include each patient only once regardless of how many adverse reactions are reported for the case. If there is more than one reaction, they are all mentioned but the case is presented according to the most serious (primary) adverse reaction. If patients experience different (unrelated) adverse reactions on different occasions, they are treated as separate reports.

Individual reports are presented in the line listings MedDRA System Organ Classes (SOCs) in the ICH E2C line-listings format (ICH E2C, 1996; EU Volume 9A, 2008). The line listings also show the case narrative, concurrent suspect and non-suspect medications, and medical history. The total number of patient cases is presented on the last page of each line listing.

The following types of cases are included in the line listings:

- Spontaneous reports

All individual case reports received spontaneously are presented. Also included are reports from the literature and regulatory authorities. Spontaneous cases associated with the product reported under the generic name are included when Novartis Consumer Health is identified as manufacturer or when the manufacturer is unknown. The spontaneous reports are presented in the following line listings and summary tabulations:

  - serious spontaneous reports in Appendix 3.1.1
  - non-serious unlisted spontaneous reports in Appendix 3.1.3
  - non-serious listed spontaneous reports in Appendix 3.1.4

- Solicited reports

There were no serious adverse reactions from studies or named-patient/compassionate use assessed as attributable to product by either investigator or sponsor (see Appendix 3.1.2 and 3.2.2).

- Non-Health Care Professional (Non-HCP) reports

Non-medically confirmed reports received from consumers/non-HCPs are presented in separate line listings presented in the same order as the medically confirmed reports (Appendix 3.2.1 to 3.2.4). Non-HCP reports, which on follow-up are confirmed by a HCP, will be handled as HCP reports.

Summary tabulations

- Aggregate summary tabulation of events received during the PSUR period

Aggregate summary tabulations of spontaneous and serious suspected solicited events reported in the PSUR period by MedDRA System Organ Class are presented in Appendix 3.3.1 for HCP reports and Appendix 3.3.2 for non-HCP reports. The tabulations show listedness and seriousness according to event level assessment as assessed at the time of receipt of the report. The tabulations show leading diagnoses, as well as signs and symptoms reported as related to the diagnoses. Related signs and symptoms will receive the same listedness assessment as the leading diagnosis to which they are related.

- Cumulative summary tabulation

Because for Zymafluor, only case level assessment of seriousness and listedness (no event assessment) is available for cases received prior to November 2002, a cumulative summary tabulation based on event level assessment cannot be provided. Therefore, a cumulative summary tabulation with preferred MedDRA terms for **all** events from all serious unlisted spontaneous reports and serious unlisted attributable clinical trial reports included in the safety database until data lock point is presented in Appendix 3.4.1 for HCP reports and Appendix 3.4.2 for non-HCP reports. It should be noted that the cumulative summary tabulations include all events reported in serious unlisted cases, regardless of whether the individual events were assessed as listed or unlisted, serious or non-serious. In addition, the tabulations include all diagnoses as well as related signs and symptoms from individual serious unlisted reports.

6.2 Overview

Distribution of cases by report type:

A total number of 55 cases were reported during the review period. Details on the distribution of the cases are presented in Table 6-1.

Table 6-1 Overview of reported cases by report type

Type of Report	Serious				Non-serious				Total	
	Unlisted		Listed		Unlisted		Listed			
	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP
Spontaneous	3	0	0	0	15	4	18	15	36	19
Solicited	0	0	0	0	0	0	0	0	0	0
Total	3	0	0	0	15	4	18	15	36	19

All adverse event reports are summarized in line listings presented in Appendices 3.1 (HCP reports) and 3.2 (non-HCP reports).

Distribution of events by MedDRA SOC:

A total of 138 reactions were reported in the 55 cases.

The distribution of the reactions by MedDRA System Organ Class (SOC) is presented in Table 6-2.

Within each MedDRA SOC the number of serious and non-serious, and unlisted and listed reactions are presented according to event level assessment. Health care professional (HCP) reports are separated from non-health care professional/consumer reports (non-HCP).

Table 6-2 Distribution of adverse reactions by MedDRA System Organ Class

MedDRA System Organ Class	Total	Serious spontaneous reactions			Non-serious reactions		
		Unlisted	Listed	Unknown	Unlisted	Listed	Unknown

		HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP	HCP	Non-HCP
Blood and lymphatic system disorders	**4**	2	0	0	0	2	0	0	0	0	0	0	0
Eye disorders	**1**	0	0	0	0	0	0	1	0	0	0	0	0
Gastrointestinal disorders	**16**	1	0	0	0	0	0	12	0	2	1	0	0
General disorders and administration site conditions	**31**	1	0	0	0	0	0	5	2	11	12	0	0
Immune system disorders	**0**	0	0	0	0	0	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	**57**	1	0	0	0	0	0	0	2	34	20	0	0
Investigations	**4**	1	0	0	0	1	0	2	0	0	0	0	0
Metabolism and nutrition disorders	**1**	0	0	0	0	0	0	1	0	0	0	0	0
Musculoskeletal and connective tissue disorders	**3**	0	0	0	0	0	0	3	0	0	0	0	0
Nervous system disorders	**2**	0	0	0	0	0	0	2	0	0	0	0	0
Psychiatric disorders	**5**	0	0	0	0	0	0	5	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	**2**	0	0	0	0	0	0	2	0	0	0	0	0
Skin and subcutaneous tissue disorders	**10**	0	0	0	0	0	0	6	1	0	3	0	0
Social circumstances	**0**	0	0	0	0	0	0	0	0	0	0	0	0
Vascular disorders	**2**	0	0	0	0	0	0	2	0	0	0	0	0
Total	**138**	**6**	**0**	**0**	**0**	**3**	**0**	**41**	**5**	**47**	**36**	**0**	**0**

For an aggregate overview of the distribution of reported events by MedDRA SOC, reference is made the summary tabulations presented in Appendix 3.3.1 (HCP reports) and 3.3.2 (non-HCP reports).

6.3 Analysis of individual case histories

In view of the small number of case reports received, all serious unlisted cases, are summarized below in Chapter 6.3.1. Also reviewed are any cases presenting relevant safety findings identified in the previous PSUR (Chapter 6.3.2) and any new relevant safety findings (Chapter 6.3.3), for which an overall safety evaluation is presented in Chapter 9.

In addition, any other noteworthy cases identified as such as because of a cluster of reports of unlisted events and/or changes in characteristics of listed events and/or data pointing at a causal relationship with the product are presented in Chapter 6.3.4.

Finally, serious cases initially reported prior to the current review period which had significant follow-up received during the review period of this PSUR are presented in Chapter 6.3.5.

6.3.1 Serious unlisted cases

No cases with fatal outcome were received.

Cases involving serious unlisted events (see Appendix 3) are presented below ordered by MedDRA SOC of the most serious/primary event.
All cases were received from HCPs.

- Blood and lymphatic system disorders (n = 1)

[redacted]Health Authority report): An 8-month-old baby was treated with Zymafluor (treatment dates and dosage not reported). The baby experienced fever and cough due to teeth eruption. The baby was treated with Doliprane (paracetamol), helicidine and Advil (ibuprofen). On an unspecified date, the baby was pallid and was hospitalized. **Pancytopenia** was diagnosed and a Myelogram revealed a global hypoplasia. The baby was treated with blood transfusion, Tazocillin (piperacillin, tazobactam) and gentamycin which led to a rapid decrease of fever. At the time of the report, pancytopenia and marrow hypoplasia were still persisting. Suspected concomitant medications (ibuprofen and paracetamol) provided a possible explanation for the reported adverse events.

B

- Gastrointestinal disorders (n = 1)

[redacted]A young patient experienced **dental fluorosis** while under treatment with Zymafluor. The final outcome was unknown. The available information was considered inadequate to fully assess the case.

In addition to the above case, one non-serious medically confirmed report [redacted]of dental fluorosis in the upper lateral left incisor and lower right incisor was reported in a 6-year-old autistic girl. Two of her teeth also presented pigmentation signs and whitish opaque blotches. The information in this case remained minimal, not allowing an adequate assessment of the case.

B

- Investigations (n = 1)

[redacted] literature report): A female patient, with a history of anorexia and family history of osteoporosis, was treated with sodium fluoride for two years. Following sodium fluoride use, the patient experienced a rapid increase in bone mineral density. While under treatment, the patient was diagnosed with osteoporosis. Two years after the last intake of sodium fluoride, the patient experienced her first fracture followed by multiple low impact or spontaneous fractures. Osteoporosis medications were replaced by teriparatide, calcium and vitamin D and her bone turnover increased. One year later, the patient presented **decreased bone mineral density**. A urine sample revealed an elevated level of sodium fluoride during teriparatide administration. After 24 months on teriparatide therapy, the patient received ibandronic acid. At one year follow-up, she had experienced no fractures and her bone mineral density had stabilized. The authors commented that the multiple peripheral fractures and high lumbar bone mineral density were associated with the previous sodium fluoride therapy and the increased bone turnover due to a paradoxical decrease in the bone density and breakdown of sodium fluoride containing bone tissue was associated with teriparatide therapy. The available information was considered inadequate to fully assess the case.

6.3.2 Relevant safety findings identified in previous PSUR

In the previous PSUR, three events (in a single case) namely loss of consciousness, dyspnea, and cyanosis have been identified as relevant safety findings. A search using MedDRA (version 11.1) High Level Terms (HLT) "Disturbances in consciousness NEC" and "Breathing abnormalities" and the SOC "Cardiac disorders" produced no reports received during the review period. Reference is made to Chapter 9.1 for a cumulative analysis of these three events.

6.3.3 New relevant safety findings

Following the analysis of the adverse event reports received during the review period, no new relevant safety findings were identified.

6.3.4 Other noteworthy cases

Cases of tooth discoloration and dental fluorosis were considered noteworthy for presentation but were not identified as relevant safety findings.

During the review period, a total of 5 cases contained reports of tooth discoloration and dental fluorosis. Tooth discoloration was reported in 3 cases, dental fluorosis was reported in 1 case and both dental fluorosis and tooth discoloration were reported in one case. All 5 reports were medically confirmed. One report of dental fluorosis was considered serious and the other cases were non-serious. All 5 cases are presented below.

[redacted] serious): This case contained scanty information on a young patient (age and gender not reported) who experienced dental fluorosis while under treatment with Zymafluor (dosage and treatment duration unknown). The outcome was unknown.

[redacted] and [redacted] These 2 cases were received from the same reporter and concerned children (ages not specified) who while being treated with Zymafluor developed a yellowish coating on their teeth which could be scratched off. Treatment with Zymafluor was continued in both cases and the outcome was unknown in both cases.

[redacted] Report of brownish teeth mottling in a 7-year-old child treated with Zymafluor (dosage and treatment duration unknown). The outcome was reported as "condition unchanged".

[redacted] Report of dental fluorosis in the upper lateral left incisor and lower right incisor was in a 6-year-old autistic girl. Two of her teeth also presented pigmentation signs and whitish opaque blotches. The outcome was not reported.

The information available in these 5 cases was considered inadequate to fully assess the cases. To further analyze the events 'tooth discoloration' and 'dental fluorosis', a cumulative search was performed and is presented in Chapter 9.3.

6.3.5 Cases with relevant follow-up

Cases initially reported prior to the review period which had significant and relevant follow-up received during the review period of this PSUR were analyzed. Those cases presenting significant follow-up relevant to the interpretation of the cases are described below. These cases are not included in the line listings in Appendices 3. Pregnancy cases with significant follow-up are presented in Chapter 9.8.

[redacted] (Non-HCP): Following internal review, follow-up was created to upgrade this case to medically significant. A female patient (age not reported) was treated with Zymafluor 1 mg from the age of 6 to 12 years. She developed brown spots and "uneven surface (incisors)" on one tooth at the age of 15 years. At the age of 35, the "below second and third teeth" were also affected. The outcome was unknown. The available information was considered inadequate to fully assess the case.

7 Studies

7.1 Newly analyzed studies with relevant safety findings

No targeted safety studies were completed during the review period.

7.2 New targeted safety studies planned, initiated or continuing during the reporting period

No new targeted safety studies were planned, initiated or continuing during the reporting period.

7.3 Published safety studies with relevant safety findings

The scientific and medical literature over the review period was screened for publications containing important new safety information associated with Zymafluor.

No publications containing important safety findings with potential impact on the product information were found.

8 Other information

8.1 Efficacy-related information

No relevant lack of efficacy reporting, which might represent a significant hazard to the treated population, was identified during the review period.

8.2 Late breaking information

No new information, which would have a significant impact on the conclusions of the overall safety evaluation, has been received since data lock point.

9 Overall safety evaluation

The data was analyzed and assessed with regard to significance and from the perspective of cumulative experience. Attention was given to serious unlisted events, non-serious unlisted events, as well as changes in characteristics of listed events and possible increases in the reporting frequency of listed events (see Chapters 9.1 - 9.4). A cumulative summary tabulation with serious unlisted reactions in the safety database is presented in Appendix 3.4.

No reports with a fatal outcome were received during the review period.

9.1 Relevant safety findings from previous PSUR

Loss of consciousness, dyspnea and cyanosis were identified in the previous PSUR on Zymafluor as relevant safety findings requiring close monitoring.

9.1.1 Loss of consciousness, dyspnea and cyanosis

New data received during the review period

No new reports of loss of consciousness, dyspnea or cyanosis were received during the review period.

Cumulative analysis

A cumulative search of the database for reports of loss of consciousness, dyspnea and cyanosis (see Chapter 6.3.2 for search criteria), retrieved a total of three cases, all of which were medically confirmed.

In one report, loss of consciousness was associated with cyanosis and dyspnea. This case describes a 17-month-old baby who took a tablet of Zymafluor and 30 to 40 seconds later she could not breathe, had blue lips and fingers and was without reaction and weak. The child used to take the crushed tablet; this was the second time she took the whole tablet. Her mother who is a nurse took emergency measures and the girl recovered. The second case is a report of dyspnea associated with urticaria in a 52-year-old female patient and the third case is a report of syncope in a 7-year-old boy. No other information was available in all 3 cases.

Conclusion

No new cases of loss of consciousness, dyspnea or cyanosis were received during the review period and the available cumulative data does not suggest a causal relationship with the

product. Therefore loss of consciousness, dyspnea and cyanosis are no longer considered relevant safety findings.

9.2 Newly identified relevant safety findings

No new relevant safety findings were identified during the review period.

9.3 Area of special interest

Tooth discoloration and dental fluorosis

A total of 5 cases of tooth discoloration and dental fluorosis were received during the review period. In order to further analyze these events, a cumulative search of the database was performed.

A cumulative search using MedDRA HLT "Dental surface disorders" and Preferred Term (PT) "Tooth disorder" produced a total of 36 cases including 3 serious cases. This includes the 5 cases received during the current review period. All 36 cases are presented in Table 9-1.

Table 9-1 Cases of tooth discoloration and dental fluorosis received since market introduction

Case N°	Serious?	Age/sex	Dose/ Indication	Treatment duration	Tooth discoloration (verbatim)	Dental fluorosis	Outcome	Medical history/ Comments
Medically validated (HCP)								
[redacted]	N	10 Y / F	1 mg/ caries prophylaxis	15 days	Teeth yellow	No	Complete recovery	
[redacted]	N	8 Y / M	1 mg/ caries prophlylaxis	60 days	Teeth yellow	No	Condition unchanged	
[redacted]	N	Unk	Unk/ Unk	Unk	Tooth discoloration	No	Unk	
[redacted]	N	2 Y / M	Unk/ Unk	Unk	Teeth yellow	No	Unk	
[redacted]	N	10 Y / F	Unk/ caries prophlylaxis	Unk	Teeth yellow	No	Complete recovery	
[redacted]	N	8 Y / M	1/ caries prophlylaxis	Unk	Tooth discoloration	No	Condition unchanged	
[redacted]	N	2 Y / F	Unk/ caries prophylaxis	900 days (2.5 Y)	Tooth discoloration	No	Condition unchanged	
[redacted]	N	Unk	Unk/ caries prophylaxis	Unk	Tooth discoloration	No	Unk	
[redacted]	N	8 Y / M	1 mg/ caries prophylaxis	49 days	Tooth discoloration	No	Unk	
[redacted]	N	6 Y / M	Unk/ caries prophylaxis	Unk	Teeth yellow	No	Unk	
[redacted]	N	F	Unk/ Unk	Unk	Tooth discoloration	No	Condition unchanged	
[redacted]	N	19 Y / M	Unk/ caries prophylaxis	Unk	Discoloration denture	No	Unk	
[redacted]	N	13 Y / M	Unk/ Unk	Unk	Tooth discoloration	No	Unk	
[redacted]	N	M	Unk/ caries prophylaxis	Unk	Tooth discoloration	No	Unk	
[redacted]	N	6 Y / F	Unk/ caries prophylaxis	3.5 years	Tooth discoloration, tooth caries aggravated	No	Condition unchanged	
[redacted]	N	9 Y / F	Unk/ caries prophylaxis	2500 d (7 years)	Teeth staining	No	Condition unchanged	
[redacted]	N	1 Y / F	Unk/ caries	Unk	Discoloration denture	No	Unk	

Case N°	Serious?	Age/sex	Dose/ Indication	Treatment duration	Tooth discoloration (verbatim)	Dental fluorosis	Outcome	Medical history/ Comments
			prophylaxis					
[redacted]	N	7 Y / M	Unk/ caries prophylaxis	7 Years	Enamel mottling	No	Condition unchanged	
[redacted]	N	F	1 mg/ Unk	Unk	Teeth yellow	No	Condition improving	
[redacted]	N	6 Y / M	Unk/ Unk	2 years	N/A	Yes	Unk	
[redacted]	N	6 Y / M	Unk/ Unk	2 years	N/A	Yes	Unk	
[redacted]	N	7 Y / F	1 mg/ dental disorder prophylaxis	7 years 3 months	White stains	Yes	Not reported	
[redacted]	N	M	Unk/ dental disorder prophylaxis	Unk	N/A	Yes	Unk	Hypersensitivity to grass, pollen and dust mite
[redacted]	N	M	Unk/ dental disorder	Unk	Whitish spots or yellow-brownish compact discoloration	Yes	Unk	Congenital oral malformation: Dysgnathia (surgical correction was planned)
[redacted]	N	8 Y	Unk/ dental disorder prophylaxis	Unk	Whitish discoloration with porous surface, arthralgia	No	Unk	Epilepsy
[redacted]	N	5 Y / M	Unk/ dental disorder prophylaxis	Unk	Grayish coating on teeth, coating on teeth, which could only be removed with fingernail not toothbrush	No	Complete recovery	Positive dechallenge and positive rechallenge
[redacted]	Y	7 Y / M	Unk/ prophylaxis	Unk	Mottled teeth, enamel divulsion, permanent discoloration	No	Condition unchanged	Health authority report
[redacted]	N	5 Y / F	0.25mg then 0.5 mg/ dental disorder prophylaxis	4 years	N/A	Yes with dental caries	Condition unchanged	Health authority report
[redacted]	Y	Young	Unk/ dental	Unk	N/A	Yes	Unk	

B

Case N°	Serious?	Age/sex	Dose/ Indication	Treatment duration	Tooth discoloration (verbatim)	Dental fluorosis	Outcome	Medical history/ Comments
			disorder prophylaxis					
[redacted]	N	7 Y	Unk/ dental disorder prophylaxis	Unk	Brownish teeth mottling	No	Condition unchanged	
[redacted]	N	Unk	Unk/ dental disorder prophylaxis	Unk	Yellowish coating which could be scratched off	No	Unk	
[redacted]	N	Unk	Unk/ dental disorder prophylaxis	Unk	Yellowish coating which could be scratched off	No	Unk	
[redacted]	N	6 Y / F	Unk/ dental disorder prophylaxis	Unk	Whitish opaque blotches, pigmentation signs	Yes	Not reported	Autism
Non-medically validated (Non-HCP)								
[redacted]	N	4 Y / F	Unk/ dental disorder prophylaxis	Unk /at least 4 months	Tooth discoloration	No	Unk	Growth retardation
[redacted]	N	6 Y / F	Unk/ dental disorder prophylaxis	Unk	Black stains on the whole dentition	No	Condition unchanged	
[redacted]	Y	F	Unk/ Unk	6 years	Brown spots, uneven surface	No	Unk	Took Zymafluor from 6-12 years. Developed brown spots and uneven surface at 15 years and 35 years

*HCP-unknown

Prevention of dental caries is the therapeutic indication for Zymafluor however, dental caries may also cause tooth discoloration. The event verbatim mostly used for tooth discoloration was more of a description of a dental plaque ("can be removed"). If dental plaque is not removed it could build a dental calculus which would make the teeth dark yellow in color (this is the most frequently reported event verbatim coded as tooth discoloration).

In addition, in the majority of these cases (29 out of 36 cases), the dose was unknown and it is clearly stated in the SPC, that: "At the doses recommended for caries prophylaxis, fluoride has not been shown to have significant side-effects". The unknown dose maybe a chronic overdosage manifested by "mottled enamel of the erupting teeth" (this is the adverse event (AE) reported in three cases).

Based on the provided information above, we can conclude that Zymafluor is not clearly related to the reported tooth discoloration and dental fluorosis. These events may have been pre-existing in line with Zymafluor's indication.

9.4 Increased frequency analysis

In the previous PSUR, PSUR 3 covering a 5-year period (estimated patient exposure: 5 million patient-years), 107 spontaneous adverse event reports were received, including 5 serious reports. This compares with 55 spontaneous adverse event reports, including 3 serious reports, in the 2 years and 10 months covered by the current PSUR, PSUR 4 (estimated patient exposure: 1.4 million patient-years).

When compensated by patient exposure, the number of adverse event reports increased from 21 to almost 38 reports per million patient treatment years. This increase may be explained by an increasing safety awareness of the health care professionals and consumers.

The total number of reported events decreased from 231 in PSUR 3 to 138 in PSUR 4. This decrease is in line with the overall decrease in number of reports.

In order to investigate possible increases in reporting incidence of individual events, the reporting frequency of events from spontaneous reports in PSUR 3 were compared with those from PSUR 4.

The table below shows the reporting frequency for each MedDRA System Organ Class (SOC), irrespective of listedness or seriousness assessment, or whether the event was reported as leading diagnosis or as a related event.

Table 9-2 Number of events reported in spontaneous cases by System Organ Class in PSUR 3 and 4

MedDRA System Organ Class	PSUR 3		PSUR 4	
	Absolute number of events	Number of events per million patient-years	Absolute number of events	Number of events per million patient-years
Blood and lymphatic system disorders	0	0.00	4	2.76
Cardiac disorders	1	0.20	0	0.00
Eye disorders	0	0.00	1	0.69

MedDRA System Organ Class	PSUR 3		PSUR 4	
	Absolute number of events	Number of events per million patient-years	Absolute number of events	Number of events per million patient-years
Gastrointestinal disorders	39	7.79	16	11.02
General disorders and administration site conditions	71	14.18	31	21.35
Injury, poisoning and procedural complications	105	20.98	57	39.26
Investigations	0	0.00	4	2.76
Metabolism and nutrition disorders	1	0.20	1	0.69
Musculoskeletal and connective tissue disorders	2	0.40	3	2.07
Nervous system disorders	2	0.40	2	1.38
Psychiatric disorders	1	0.20	5	3.44
Respiratory disorders	2	0.40	2	1.38
Skin and subcutaneous tissue disorders	7	1.40	10	6.89
Vascular disorders	0	0.00	2	1.38
Total number of events	231	46.15	138	95.05
Total number of spontaneous patient reports	107	21.38	55	37.88

Noteworthy increases in the absolute number of individual events were further analyzed for changes in reporting incidence per million patient-years. An analysis of individual events reveals that although there was a decrease in the absolute number of events in the majority of SOCs in PSUR 4, the reporting incidence per million patient-years increased in almost all the SOCs listed below. A noteworthy increase in the reporting incidence per million patient-years was observed in the SOCs Blood and lymphatic system disorders, Gastrointestinal disorders, General disorders and administration site conditions, Injury, poisoning and procedural complications, Investigations, Psychiatric disorders and skin and subcutaneous tissue disorders. The individual events reported at significant higher incidence, were further analyzed with the following results:

The increase in reporting incidence of events under the SOC Blood and lymphatic system disorders is due to one medically confirmed serious unlisted spontaneous case in which 4 events (bone marrow failure, erythropoiesis abnormal, pancytopenia and thrombocytopenia) related to the SOC Blood and lymphatic system disorders were reported in PSUR 4 and no reports of such events in PSUR 3. Suspected concomitant medications (ibuprofen, and paracetamol) provided a possible explanation for the reported adverse events in this case (see chapter 6.3.1). No specific action was considered necessary.

The most frequently reported individual events in the SOC Gastrointestinal disorders in PSUR 3 and 4, respectively, were abdominal pain (3-1), dental fluorosis (6-2), nausea (6-0) and tooth discoloration (8-4). Abdominal pain was reported in a non-serious medically confirmed case, associated with fever and diarrhea after a 2-year-old girl ingested several tablets of Zymafluor. The physician stated that the reaction was not related to Zymafluor, but was probably due to an acute gastritis. The two cases of dental fluorosis reported during the review period were received from healthcare professionals (see chapter 6.3.1). One case was

considered serious and the other non-serious. However, in both cases, the information was considered inadequate to fully assess the case. Concerning the reports of tooth discoloration, all 4 reports were received from healthcare professionals and were considered non-serious. In one case, tooth discoloration was reported as a symptom of dental fluorosis. Two other cases of tooth discoloration were received from the same reporter. These two cases concerned children (ages not specified) who had a yellowish coating on their teeth which could be scratched off. The dosage and duration of treatment was not provided in both cases. The fourth case of tooth discoloration concerns a 7-year-old child who developed a brownish mottling of the teeth. The dosage and duration of treatment was not reported. No specific action was considered necessary.

The most frequently reported event in the SOC General disorders and administration site conditions in PSUR 3 and 4 respectively was "no adverse event" (66-23). No adverse event is coded when no adverse event is reported in cases of accidental exposure, medication error or overdose (chapter 9.6 and chapter 9.11). No specific action was considered necessary.

The most frequently reported individual events in the SOC Injury poisoning and procedural complications in PSUR 3 and 4 respectively were accidental drug intake by child (10-26), accidental exposure (22-0), accidental overdose (63-16), incorrect dose administered (4-5) and overdose (3-5). These cases are addressed in chapter 9.6 (experience with overdose) and chapter 9.11 (prescription and medication errors). No specific action was considered necessary.

The increase in reporting incidence of events under the SOC Investigations is due to 4 events reported in two medically confirmed serious unlisted cases in PSUR 4 and no reports of such events in PSUR 3. In one case, 1 event (neutrophil count abnormal) was reported as a symptom of bone marrow failure (see chapter 6.3.1). The other 3 events (biopsy bone abnormal, bone density decreased and fluoride increased) were reported in a single literature report which is presented in chapter 6.3.1. No specific action was considered necessary.

Although there was an increase in the reporting incidence per million patient-years in the SOC Psychiatric disorders from 0.20 to 3.44 in PSUR 3 and 4 respectively, there was no significant increase in individual events. The reported events in PSUR 3 and 4 respectively were crying (0-2), nervousness (1-1), restlessness (0-1) and stress (0-1). No specific action was considered necessary.

An increase in the reporting incidence per million patient-years from 1.40 to 6.89 in PSUR 3 and 4 respectively was observed in the SOC Skin and subcutaneous tissue disorders. However, despite the increase in reporting incidence, no increase in any individual event was noted. The events which were reported more than once in either PSUR 3 or 4 respectively were hyperhydrosis (0-2), urticaria (2-1) and xeroderma (2-0). No specific action was considered necessary.

Conclusion:

No specific reasons, other than the general causes described above, could be identified for the increased reporting rates in individual listed events but the data does not require a modification of the frequencies mentioned in the SPC.

In conclusion, compared with the previous update, the increase in the frequency of individual listed events reviewed during this period did not reflect a meaningful change in occurrence and does not require a modification of the information presented in the SPC.

9.5 Drug interactions

No reports of drug interactions were received during the review period.

9.6 Experience with overdose (deliberate or accidental) and its treatment

There were 24 reports recorded as overdose during the period under review, including 13 reports from HCPs. No adverse event was reported in 20 out of 24 cases. The cases are summarized in Table 9-3.

Table 9-3 Reports of overdose received during the current review period

Case IDs	Age/ Sex	Zymafluor dose taken	Adverse Event	Outcome	Comment
HCP reports					
[redacted]	2Y / F	Several 1 mg tablets	Gastritis (unlisted), pyrexia (unlisted) colic (listed)and diarrhea (listed).	Complete recovery	A consulting physician stated that the reaction was not related to Zymafluor, but was probably due to acute gastritis
[redacted]	2Y / F	Half a vial	Vomiting (listed)	Complete recovery	The reporter considered that the event was not related to the drug.
[redacted]	2Y / Unk	20 tablets of 0.25 mg (5 mg)	No adverse event reported	Not applicable	
[redacted]	2Y / F	5 tablets of 0.25 mg	No adverse event reported	Not applicable	
[redacted]	33M / M	25 mg (contents of half a bottle of 0.5 mg tablets)	No adverse event reported	Not applicable	
[redacted]	3Y / F	20 tablets of 0.5 mg (10 mg)	No adverse event reported	Not applicable	
[redacted]	1Y / F	1 mg per day for 2 months	No adverse event reported	Not applicable	
[redacted]	3Y / M	10 mg (20 tablets of 0.5 mg)	No adverse event reported	Not applicable	
[redacted]	3Y / F	13 tablets of 0.25 mg (3.25 mg)	No adverse event reported	Not applicable	
[redacted]	3Y /	40 mg (80	Feeling sick	Complete	The events lasted for 3 hours

Case IDs	Age/ Sex	Zymafluor dose taken	Adverse Event	Outcome	Comment
[redacted]	Male	tablets of 0.25 mg). 2.5 mg / kg	(unlisted), bad taste (unlisted), crying (unlisted) and gastric pain (listed)	recovery	
[redacted]	23M / F	Unknown	No adverse event reported	Not applicable	
[redacted]	6Y / F	40 tablets of 0.5 mg (20 mg)	No adverse event reported	Not applicable	
[redacted]	6Y / F	40 tablets of 0.5 mg (20 mg)	No adverse event reported	Not applicable	
Non-HCP reports					
[redacted]	2Y / M	100 tablets of 0.25 mg (25 mg)	Soft stools (listed)	Complete recovery	
[redacted]	Unk / M	30 tablets of 0.25 mg (7.5 mg)	No adverse event reported	Not applicable	
[redacted]	2Y / M	0.5 mg daily instead of 0.25 mg for 7 months	No adverse event reported	Not applicable	
[redacted]	2Y / M	3 tablets	No adverse event reported	Not applicable	
[redacted]	Unk / Unk	Too many tablets	No adverse event reported	Not applicable	
[redacted]	Unk / F	10 mg daily	No adverse event reported	Not applicable	
[redacted]	3Y / Unk	150 - 170 tablets	No adverse event reported	Not applicable	
[redacted]	2.5Y / M	30 tablets of 0.5 mg (15 mg)	No adverse event reported	Not applicable	The child was treated with domperidone
[redacted]	2Y / F	10 tablets of 0.25 mg (2.5 mg)	No adverse event reported	Not applicable	
[redacted]	3Y / Unk	90 tablets of 0.25 mg (22.5 mg)	No adverse event reported	Not applicable	
[redacted]	Unk / F	1 mg per day instead of 0.25 mg for 9 months	No adverse event reported	Not applicable	

Unlisted events were reported in two medically confirmed cases, namely gastritis, pyrexia, feeling sick, bad taste and crying. In all other cases either listed non-serious events, or no events were reported. Therefore the information in the overdose cases does not necessitate a modification of the 'Overdose' section in the SPC.

9.7 Drug abuse or misuse

Two cases containing reports of drug misuse were received during the review period. Both cases were received from non-HCPs and are reports of overdose in a 2 and 3 year-old child. The 2 year-old ([redacted] took 10 tablets of 0.25 mg (2.5 mg) and the 3 year-old ([redacted] took 90 tablets of 0.25 mg (22.5 mg). No adverse event was reported in both cases.

The information in the drug misuse cases does not necessitate a modification of the SPC.

9.8 Positive or negative experience during pregnancy or lactation

Positive or negative experiences during pregnancy are presented for the current PSUR period (Chapter 9.8.1) and cumulatively (Chapter 9.8.2). Data collected prospectively (acquired prior to the knowledge of the pregnancy outcome or prior to the detection of a congenital malformation at prenatal examination e.g. fetal ultrasound, serum markers) are separated from data collected retrospectively (acquired after the outcome of the pregnancy is known or after the detection of a congenital malformation on prenatal test).

9.8.1 Data for reporting period

9.8.1.1 Drug exposure during pregnancy

Prospective

During the review period there were 2 medically confirmed prospective reports of drug exposure during pregnancy.

[redacted]: A 27-year-old woman in her 7th month of pregnancy was prescribed Zymafluor 1 mg per day for "protection of her very spoiled teeth".

[redacted]: A 21-year-old woman in her 5th month of pregnancy was prescribed Zymafluor for caries prophylaxis.

No adverse event was reported in both cases and the outcome of both pregnancies was unknown despite follow-up attempts.

Retrospective

During the review period there were no retrospective reports of drug exposure during pregnancy.

9.8.2 Cumulative data

Cumulatively there have been 2 prospective and 2 retrospective cases.

This includes reports collected since the international birth date (IBD) of the product at a time when procedures for collection of reports of exposure during pregnancy were different and sometimes less stringent than the current procedures. Particularly the distinction between prospective and retrospective cases may not always have been recorded correctly in the sense that some of the legacy cases presented in the table below and marked as retrospective may actually have been initially received as prospective cases.

Table 9-4 Summary table of pregnancy outcome

Pregnancy outcome	Prospective cases (number)					Retrospective cases (number)				
	Timing of exposure in pregnancy (trimester)					Timing of exposure in pregnancy (trimester)				
	Before concept -tion	1st	After 1st	All	Unk	Before concep- tion	1st	After 1st	All	Unk
Outcome unknown	0	0	2	0	0	0	0	0	0	2
Total	**0**	**0**	**2**	**0**	**0**	**0**	**0**	**0**	**0**	**2**

9.8.3 Conclusion on pregnancy and lactation cases

Taking the relatively small number of reports of exposure during pregnancy into account, the cumulative analysis of pregnancy cases did not provide evidence indicating that the product causes any specific fetal defect or congenital anomaly.

As is indicated in the SPC, Zymafluor has been in wide use during pregnancy for many years at a recommended dose of 1 mg / day without apparent consequence.

As stated in the SPC, the resultant content of fluoride ion in maternal milk is negligible.

9.9 Experience in special patient groups

No meaningful new information on the experience in special patient groups was identified during the review period.

An analysis of the indications presented in the adverse event reports received during the review period did not reveal any significant off-label use.

An analysis of the age groups presented in adverse event reports did not reveal any specific issue with regard to specific age groups, including use in the pediatric population.

9.10 Effects of long term treatment

No meaningful new information on the effects of long term treatment was identified during the review period.

9.11 Prescription and medication errors

A search for MedDRA version 11.1 High Level Group Term (HLGT) Medication Error (excluding preferred terms associated with drug interactions [addressed in Chapter 9.5], intentional overdose [addressed in Chapter 9.6], drug abuse or misuse [addressed in Chapter 9.7] and drug exposure during pregnancy [addressed in Chapter 9.8]) produced 31 cases describing 48 medication errors received during the review period. Out of 31 cases, adverse events were reported in 5 cases including 4 cases from healthcare professionals. Accidental drug intake was reported 26 times, accidental overdose was reported 16 times, incorrect dose administered was reported 5 times and overdose was reported once. The 5 cases in which adverse events were reported are presented below:

Medically confirmed cases (n = 4)

[redacted] A 2-year-old female patient accidentally ingested half a vial of Zymafluor 0.114%. The child experienced vomiting within 30 seconds post ingestion. The vomiting lasted for 1 minute. The child was given milky products and completely recovered. The reporter considered that the event was not related to Zymafluor.

[redacted] A 2-year-old female patient took several tablets (exact amount unknown) of Zymafluor 1 mg and experienced colic, diarrhea and fever during the night. She was seen by a physician because the events lasted for several days. The physician stated that the reaction was probably due to acute gastritis and was not related to Zymafluor. The child completely recovered.

[redacted] A 2-year-old girl ingested half a bottle of Zymafluor 0.114%. A physician was consulted 4 days later. The examination revealed an orange-yellow colored tongue. The orange coloration of the tongue persisted for 3 weeks after which the child completely recovered.

[redacted] A 3-year-old boy ingested 80 Zymafluor 0.5 mg tablets (2.5 mg/kg). He complained of gastric pain, feeling sick, bad taste and he cried. Treatment with Zymafluor was discontinued. He was given milky products. The events lasted for 3 hours and the child completely recovered.

Non-medically confirmed cases (n = 1)

[redacted]: Report of soft stools in a 2-year-old boy 3 hours after ingestion of about 100 tablets of Zymafluor 0.25 mg (2.27 mg/kg). He was given milky products within one hour after ingestion of Zymafluor. The child completely recovered the next day.

Cumulatively, there have been 177 reports describing 223 medication errors distributed as shown in Table 9-5.

Table 9-5 Cumulative overview of medication errors

Medication error PT	Number of HCP reports	Number of non-HCP reports
Accidental drug intake by child	23	13
Accidental exposure	14	8
Accidental overdose	101	42
Accidental poisoning	6	0
Drug administration error	1	0
Incorrect dose administered	5	4
Multiple drug overdose accidental	1	0
Overdose	1	3
Wrong drug administered	0	1
Total	**152**	**71**

Cumulatively, unlisted events in medication error cases reported by healthcare professionals consist of gastritis (1 report), pyrexia (3 reports), tongue discoloration (1 report), malaise (1 report), dysguesia (1 report), crying (1 report) and hypercalcemia (1 report).

Based on the information in the medication error cases, no specific action was considered necessary.

10 Conclusion

In the previous PSUR, three events namely loss of consciousness, dyspnea, and cyanosis have been identified as relevant safety findings.

A cumulative search of the database for reports of loss of consciousness, dyspnea and cyanosis, retrieved a total of 3 reports, all of which were medically confirmed. In one report, loss of consciousness was associated with cyanosis and dyspnea. The database also contains one other case of syncope and one of dyspnea associated with urticaria. No new cases were received during the review period and the available data does not suggest a causal relationship with the product. Therefore loss of consciousness, dyspnea and cyanosis are no longer considered relevant safety findings.

No new relevant safety findings were identified. The safety data remains in accord with the previous cumulative experience and the safety information presented in the SPC.

11 References

[Bonavitacola A (2008)] Zymafluor, Periodic Safety Update Report 3. Period covered: 01 April 2001 - 31 March 2006. Issued: 24 May 2006.

[EU Volume 9A (2008)] Volume 9A of the Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use.

[ICH E2C (1996)] Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.

[ICH E2C (2003)] Addendum to ICH E2C. Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.

Appendices

Appendix 1 Core Data Sheet

NOVARTIS

Novartis Consumer Health SA
CH-1260 Nyon, Switzerland

Global Drug Regulatory Affairs

ZYMAFLUOR® ¼ mg Tablets
ZYMAFLUOR® ½ mg Tablets
ZYMAFLUOR® ¾ mg Tablets
ZYMAFLUOR® 1 mg Tablets
ZYMAFLUOR® Drops

Summary of Product Characteristics

Author:	[redacted]
Document type:	Core SPC
Document status:	Final
Release date:	05 Dec 2006
Number of pages:	10

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TABLE OF CONTENTS

1. NAME OF THE MEDICINAL PRODUCT

Zymafluor® ¼ mg Tablets

Zymafluor® ½ mg Tablets

Zymafluor® ¾ mg Tablets

Zymafluor® 1 mg Tablets

Zymafluor® Drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zymafluor®	**Tablets**				**Drops***	
Strength	¼ mg	½ mg	¾ mg	1 mg	%m/V	20 ml
Sodium Fluoride	0.55 mg	1.105 mg	1.658 mg	2.2 mg	0.252	50 mg
Equivalent fluoride	0.25 mg	0.5 mg	0.75 mg	1 mg	0.114	23 mg

*Zymafluor® Drops: 1 ml = 18 drops

3. PHARMACEUTICAL FORM

Zymafluor® Tablets

Tablet

Zymafluor® Drops

Oral drops

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Prevention of dental caries

4.2. Posology and method of administration

The daily dosage should be adjusted to the age of the child as well as to the fluoride content of drinking water and to fluorides ingested from other sources such as from the diet and fluoride toothpastes.

The doses given in the following table are those recommended with the necessary adjustment depending on the fluoride content of the local water supply:

Concentration of fluoride in drinking water (mg/l)	<0.3	0.3 - 0.7	>0.7
Recommended fluoride supplementation	mg/F^-/day (drops of Zymafluor®)		
Age			
2 weeks to 2 years	0.25 (4 drops)	0	0
2 to 4 years	0.50 (8 drops)	0.25 (4 drops)	0
4 to 16 years	1.00 (16 drops)	0.50 (8 drops)	0
In pregnant women	1.00 (16 drops)	0.50 (8 drops)	0

Zymafluor® is usually given as a single daily dose.

Zymafluor® Tablets

In infants the tablets should be crushed and diluted in some water, tea or fruit juice, but not in milk.

As soon as the age of the child permits, Zymafluor® Tablets should no longer be swallowed, but sucked slowly in the mouth, between the cheek and gum, sometimes on the left and sometimes on the right side. They are best taken in the evening before bedtime, after brushing the teeth as, in this way, high fluoride concentrations in the mouth can be maintained for a longer period.

Zymafluor® Drops

The drops can be administered as such or diluted in some water, tea or fruit juice, but not in milk.

Zymafluor® Drops has been developed to facilitate administration in infants (2 weeks to 2 years). In children over 2 years, although Zymafluor® Tablets are better adapted, Zymafluor® Drops may nevertheless be given at the doses indicated above.

4.3. Contra-indications

Hypersensitivity to any of the constituents.

4.4. Special warnings and special precautions for use

When considering fluoride supplementation, allowance should be made for fluorides ingested from other sources so as to avoid overdosage.

In areas where table salt or water is fluoridated, the dosage of Zymafluor® should be reduced. If the water contains more than 0.7 mg/l of fluoride, supplementation is not recommended.

4.5. Interactions with other medicaments and other forms of interaction

The absorption of fluoride is related to the solubility of the compound ingested, absorption is inhibited by calcium, magnesium or aluminium. Zymafluor® should therefore not be given with milk and dairy products nor with antacids containing calcium, aluminium or magnesium salts.

4.6. Pregnancy and lactation

During pregnancy Zymafluor® has been in wide use for many years at a recommended dose of 1 mg/day without apparent consequence. The resultant content of fluoride ion in maternal milk however is negligible and the breast-fed baby should be given 0.25 mg fluoride daily.

4.7. Effects on ability to drive and use machines

Zymafluor® has no influence on ability to drive or use machinery.

4.8. Undesirable effects

At the doses recommended for caries prophylaxis, fluoride has not been shown to have significant side-effects. However rare cases of mild skin rashes (erythema, urticaria) have been reported. They disappear rapidly on stopping treatment.

4.9. Overdose

Chronic overdosage

The major manifestation of a chronic ingestion of excessive amounts of fluoride, for example 2 mg of fluoride per day during the years (approximately 16 years) necessary for calcification of the enamel of the teeth, is mottled enamel of the erupting teeth.

Acute overdosage

Symptoms of acute overdosage have been reported when more than approx. 100 mg of fluoride have been ingested.

i.e. in an adult approximately:

400 Zymafluor® ¼ mg tablets

200 Zymafluor® ½ mg tablets

150 Zymafluor® ¾ mg tablets

100 Zymafluor® 1 mg tablets

100 ml (5 bottles) Zymafluor® drops.

The lethal dose in adults (70 kg) is stated to be between 2.2 g - 4.5 g fluoride. In 10 kg children approx. 200 mg fluoride may be fatal.

i.e. approximately:

900 Zymafluor® ¼ mg tablets

450 Zymafluor® ½ mg tablets

300 Zymafluor® ¾ mg tablets

200 Zymafluor® 1 mg tablets

200 ml (10 bottles) Zymafluor® drops.

The initial symptoms are largely related to gastro-intestinal intolerance: salivation, nausea, abdominal pain, vomiting and diarrhoea. These may be followed by muscular weakness, chronic convulsions, respiratory, cardiac and renal failure.

Death may occur within 2-4 hours.

Hypocalcaemia and hypoglycaemia are frequent findings.

Treatment:

- If less than 5.0 mg/kg body weight of fluoride ion has been ingested

  i.e. for a 10 kg child less than:

  200 Zymafluor® ¼ mg tablets

  100 Zymafluor® ½ mg tablets

  60 Zymafluor® ¾ mg tablets

  50 Zymafluor® 1 mg tablets

  40 ml (2 bottles) Zymafluor® drops.

  - Give calcium orally (milk) to relieve gastro-intestinal symptoms, and observe for a few hours.

- If more than 5.0 mg/kg body weight has been ingested

  i.e. for a 10 kg child more than:

  200 Zymafluor® ¼ mg tablets

  100 Zymafluor® ½ mg tablets

  60 Zymafluor® ¾ mg tablets

  50 Zymafluor® 1 mg tablets

  40 ml (2 bottles) Zymafluor® drops.

- Induce vomiting.
- Give soluble calcium orally in any form (e.g. milk, 5% calcium gluconate, or calcium lactate solution).
- Observe for a few hours in the emergency department.

↳ If more than 15 mg/kg body weight of fluoride ion has been ingested

i.e. for a 10 kg child more than:

600 Zymafluor® ¼ mg tablets

300 Zymafluor® ½ mg tablets

200 Zymafluor® ¾ mg tablets

150 Zymafluor® 1 mg tablets

120 ml (6 bottles) Zymafluor® drops.

- admit immediately to a hospital facility.

The principles of the treatment are as follows:

Hospital treatment is required to empty the stomach by aspiration and lavage with lime water or a 1% solution of calcium chloride or another calcium salt to precipitate fluoride. Aluminium hydroxide administered after gastric lavage may reduce fluoride absorption. Start cardiac monitoring (observe for peaking T waves and prolonged QT intervals). Intravenous injection of 10 ml of a 10% calcium gluconate solution may be given to control convulsions and repeated every 4 to 6 hours if needed. Morphine or pethidine may be given by injection if needed, to control colic. Circulation should be maintained with infusions of suitable electrolyte solutions. Respiration may require assistance.

Haemodialysis may be used. Vomit, faeces and urine should be washed away promptly to prevent external burns.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Caries prophylactic agents, ATC code: A01AA.

Sodium fluoride enhances the resistance of teeth to caries. It may render the enamel of teeth more resistant to acid produced by the bacteria of the dental plaque which transform sugar into acid, promote remineralisation, or reduce microbial acid production. Fluoridation should begin before eruption of the teeth and should be maintained for life.

Before eruption fluoride is carried to the developing teeth by the blood stream, permitting an effective pre-eruptive fluoridation. After eruption the teeth take up fluoride by direct contact with the fluoride contained in the saliva.

5.2. Pharmacokinetic properties

Sodium fluoride is readily absorbed from the gastro-intestinal tract. The bioavailability of sodium fluoride is virtually 100%. Fluoride is a normal component of body fluids and soft tissues.

Most of the fluoride in the body is deposited in the bones and teeth. Fluoride is also present in faeces, sweat, saliva, milk, tears and hair. It is excreted mostly in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Zymafluor® ¼ mg Tablets

Sorbitol
Colloidal anhydrous silica
Peppermint oil
Magnesium stearate.

Zymafluor® ½ mg Tablets

Sorbitol
Colloidal anhydrous silica
Iron oxide yellow
Iron oxide brown
Magnesium stearate.

Zymafluor® ¾ mg Tablets

Sorbitol
Colloidal anhydrous silica
Iron oxide brown
Magnesium stearate.

Zymafluor® 1 mg Tablets

Sorbitol
Colloidal anhydrous silica
Iron oxide yellow
Magnesium stearate.

Zymafluor® Drops

Benzoic Acid
Glycerol

Sorbitol
Purified water.

6.2. Incompatibilities

No incompatibilities have been reported to date.

6.3. Shelf life

Zymafluor® ¼ mg Tablets: 36 months.

Zymafluor® ½ mg Tablets: 36 months

Zymafluor® ¾ mg Tablets: 36 months

Zymafluor® 1 mg Tablets: 60 months

Zymafluor® Drops: 60 months.

6.4. Special precautions for storage

Zymafluor® ¼ mg Tablets:

Do not store above 25°C
Store in the original package. Keep the tube tightly closed.

Zymafluor® ½ mg Tablets
Do not store above 30°C
Store in the original container in order to protect from moisture

Zymafluor® ¾ mg Tablets:
Do not store above 30°C
Store in the original container in order to protect from moisture

Zymafluor® 1 mg Tablets:
Do not store above 30°C
Store in the original container in order to protect from moisture

Zymafluor® Drops:

Do not store above 30°C

6.5. Nature and contents of container

Zymafluor® ¼ mg Tablets
Zymafluor® ½ mg Tablets
Zymafluor® ¾ mg Tablets

Zymafluor® 1 mg Tablets

- polypropylene tubes, with a polyethylene stopper and dosing cap.

Zymafluor® Drops

- 20 ml white opaque high-density polyethylene bottles, low density polyethylene pipette and polypropylene screw cap.

Pack size

Zymafluor® ¼ mg Tablets: Local.
Zymafluor® ½ mg Tablets: Local.
Zymafluor® ¾ mg Tablets: Local.
Zymafluor® 1 mg Tablets: Local.
Zymafluor® Drops: 20 ml.

6.6. Instructions for use/handling

Safety note concerning children:

Medicines should be kept out of the reach of children.

7. MARKETING AUTHORISATION HOLDER

To be completed locally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed locally

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

To be completed locally

10. DATE OF (PARTIAL) REVISION OF THE TEXT

To be completed locally

Appendix 2 - Cumulative worldwide marketing authorization status

ZYMAFLUOR (NA FLUORIDE) 0.25mg **Pharmaceutical Form:** buccal tablet

Country	Action date	Launch date	Trade name(s)	Comments
PORTUGAL	A: Jun 1950 AR: May 2005	launched	ZYMAFLUOR 1/4 MG	
SWITZERLAND	A: Jun 1950 AR: Jul 2003	Dec 1980	ZYMAFLUOR 0.25 MG	
ECUADOR	A: Jul 1952 AR: Oct 1991 V: unknown	launched	N/A	
BOLIVIA	A: Nov 1952 AR: Jun 1989 V: unknown	launched	N/A	
PERU	A: Apr 1954 AR: Sep 1986 V: unknown	launched	N/A	
EL SALVADOR	A: Sep 1954 AR: Apr 1992 V: unknown	launched	ZYMAFLUOR 1/4MG COMPRIMIDOS	
AUSTRIA	A: Mar 1955 AR: May 1998	Jun 1970	ZYMAFLUOR 1/4MG-TABLETTEN	
PARAGUAY	A: Dec 1955 AR: Mar 1988 V: unknown	launched	N/A	
PANAMA	A: Apr 1957 AR: Jan 1987 V: unknown	launched	ZYMAFLUOR 1/4MG COMPRIMIDOS	
BELGIUM	A: Oct 1961 AR: Feb 2003	launched	Z-FLUOR	
JORDAN	A: Jan 1965	launched	ZYMAFLUOR 0.25MG	

Country	Action date	Launch date	Trade name(s)	Comments
	AR: Jan 1983 V: Jan 2006			
DOMINICAN REPUBLIC	A: Apr 1969 AR: Nov 1990 V: unknown	launched	N/A	
TRINIDAD AND TOBAGO	A: Nov 1969 V: unknown	launched	ZYMAFLUOR 0.25 MG TAB	
VENEZUELA	A: Nov 1969 V: unknown	launched	ZYMAFLUOR 1/4MG COMPRIMIDOS	
ITALY	A: Jun 1971 AR: May 2005	launched	ZYMAFLUOR 0.25 MG	
ISRAEL	A: Dec 1973 AR: Jun 1999 V: Jun 2004	launched	ZYMAFLUOR	
NETHERLANDS	A: Dec 1976	launched	ZYMAFLUOR, TABLETTEN 0,25 MG	
KUWAIT	A: May 1979 V: unknown	launched	ZYMAFLUOR 1/4MG	
SRI LANKA	A: Jul 1980 V: unknown	launched	N/A	
PHILIPPINES	A: Jul 1981 AR: Oct 1997 V: unknown	Dec 1980	ZYMAFLUOR 0,25 MG	
GERMANY	A: Jul 1981	launched	FLUORID TABLETTEN 0.25MG	
BAHRAIN	A: Oct 1981 AR: Mar 1995 V: unknown	launched	ZYMAFLUOR 1/4MG	
IVORY COAST	A: Apr 1984 AR: Apr 1990 V: unknown	launched	N/A	

Country	Action date	Launch date	Trade name(s)	Comments
CAMEROON	A: Jan 1985 V: unknown	launched	N/A	
THAILAND	A: Nov 1985 AR: Feb 2004	Dec 1980	ZYMAFLUOR ¼ MG	
GUINEA	A: Apr 1986 V: unknown	launched	N/A	
BENIN	A: Apr 1986 V: unknown	launched	N/A	
SOUTH AFRICA	A: Dec 1986 AR: Oct 1984	launched	ZYMAFLUOR TABLETS	
GUATEMALA	A: Feb 1988 V: unknown	launched	ZYMAFLUOR 1/4MG COMPRIMIDOS	
TOGO	A: Nov 1988 V: unknown	launched	N/A	
IRAQ	A: Jun 1989 V: unknown	launched	N/A	
TAIWAN	A: Jul 1989 AR: Jul 2004	launched	ZYMAFLUOR 1/4MG	
D.R. CONGO	A: Oct 1989 AR: Feb 1994 V: unknown	launched	N/A	
LUXEMBURG	A: Mar 1990 AR: Feb 1982	launched	ZYMAFLUOR	
TURKEY	A: May 1990	Oct 1994	ZYMAFLUOR 0.25 MG	
U. A. EMIRATES	A: Jun 1990 AR: Jun 1990 V: Feb 2008	launched	ZYMAFLUOR 1/4MG	
YEMEN	A: Dec 1990 V: unknown	launched	N/A	
COSTA RICA	A: Jul 1991	launched	ZYMAFLUOR 1/4MG COMPRIMIDOS	

Country	Action date	Launch date	Trade name(s)	Comments
	V: Jan 2000			
UNITED KINGDOM	A: Jul 1991	none	ZYMAFLUOR TABLETS	
	AR: Dec 2005			
QATAR	A: Feb 1992	launched	ZYMAFLUOR 1/4MG	
	V: unknown			
MALTA	A: Apr 1992	launched	ZYMAFLUOR 0.25MG	
	V: unknown			
FRANCE	A: Sep 1992	Oct 1975	ZYMAFLUOR 0.25 MG	
	AR: Mar 2003			
TUNISIA	A: Dec 1993	launched	N/A	
	V: unknown			
NICARAGUA	A: unknown	launched	ZYMAFLUOR 1/4MG COMPRIMIDOS	
	AR: May 1983			
	V: Jan 2000			
ARGENTINA	A: Aug 1994	launched	ZYMAFLUOR	
	V: Aug 2004			
BULGARIA	A: Nov 1994	launched	ZYMAFLUOR TABLET 1/4MG	
	AR: Feb 2006			
HUNGARY	A: Jan 1995	launched	ZYMAFLUOR ¼ MG BUKKÁLIS TABLETTA	
	AR: Jul 2004			
SPAIN	A: Mar 1997	none	ZYMAFLUOR 0.25 MG COMPRIMIDOS	
LEBANON	A: May 1997	launched	ZYMAFLUOR	
	V: unknown			
CZECH REPUBLIC	A: Jun 1997	launched	ZYMAFLUOR 1/4 MG	
	AR: Jun 2002			
OMAN	A: Feb 1998	launched	ZYMAFLUOR 0.25MG	
	V: unknown			
POLAND	A: Jul 1998	launched	ZYMAFLUOR	

Country	Action date	Launch date	Trade name(s)	Comments
			0.25 MG	
	AR: Sep 2003			
ROMANIA	A: Aug 2000	Aug 2000	ZYMAFLUOR 1/4MG	
	AR: Jun 2005			
LAOS	A: Jan 2007	launched	ZYMAFLUOR 0.25 MG	
CAMBODIA	A: Feb 2008	none	ZYMAFLUOR 0.25MG TABLET	
CURACAO	A: unknown	launched	ZYMAFLUOR 0.25MG	
	V: unknown			
JAMAICA	A: unknown	launched	ZYMAFLUOR 1/4MG TABLETS	
	V: unknown			
HONDURAS	A: unknown	launched	ZYMAFLUOR 1/4MG COMPRIMIDOS	
	V: unknown			
CONGO	A: unknown	launched	N/A	
	AR: Jul 1990			
	V: unknown			
ALBANIA	A: unknown	launched	ZYMAFLUOR 1/4MG	
	V: unknown			
PALESTINE	A: unknown	launched	N/A	
	V: unknown			
ARUBA	A: unknown	launched	ZYMAFLUOR 0.25MG	
	V: unknown			

ZYMAFLUOR (NA FLUORIDE) 0.5mg **Pharmaceutical Form:** buccal tablet

Country	Action date	Launch date	Trade name(s)	Comments
GERMANY	A: Aug 1991	launched	ZYMAFLUOR 0.5MG	
	AR: May 2009			
FRANCE	A: Apr 1996	launched	ZYMAFLUOR 0.50 MG	
	AR: Apr 2006			
ITALY	A: Apr 2001	Sep 2002	ZYMAFLUOR	

Country	Action date	Launch date	Trade name(s)	Comments
			0.5MG TABLET	
	AR: May 2005			

ZYMAFLUOR (NA FLUORIDE) 0.75mg **Pharmaceutical Form:** buccal tablet

Country	Action date	Launch date	Trade name(s)	Comments
NETHERLANDS	A: Sep 1976	launched	N/A	
	AR: Sep 1976			
GERMANY	A: Aug 1991	launched	FLUORID-TABLETTEN 0.75MG	
	AR: May 2001			
	V: unknown			
FRANCE	A: Apr 1996	launched	ZYMAFLUOR 0.75 MG	
	AR: Apr 2006			
ITALY	A: Apr 2001	none	ZYMAFLUOR 0.75MG	
	AR: May 2005			

ZYMAFLUOR (NA FLUORIDE) 1mg **Pharmaceutical Form:** buccal tablet

Country	Action date	Launch date	Trade name(s)	Comments
AUSTRIA	A: Apr 1960	launched	ZYMAFLUOR 1MG-TABLETTEN	
	AR: May 1998			
SWITZERLAND	A: Apr 1965	Dec 1980	ZYMAFLUOR 1 MG	
	AR: Jul 2003			
LEBANON	A: Mar 1971	launched	ZYMAFLUOR	
BOLIVIA	A: Nov 1971	launched	N/A	
	AR: Jun 1989			
	V: unknown			
VENEZUELA	A: Mar 1973	launched	ZYMAFLUOR 1MG COMPRIMIDOS	
	V: Jan 2000			
ITALY	A: May 1973	Oct 2001	ZYMAFLUOR 1MG STRAWBERRY	
	AR: May 2005			

Country	Action date	Launch date	Trade name(s)	Comments
PHILIPPINES	A: Mar 1974 AR: Jul 1992 V: unknown	Dec 1980	ZYMAFLUOR 1 MG	
DOMINICAN REPUBLIC	A: Apr 1975 AR: Jun 1995 V: unknown	launched	N/A	
FRANCE	A: Nov 1976 AR: Mar 2003	Nov 1985	ZYMAFLUOR 1 MG	
PANAMA	A: Aug 1978 AR: Jan 1987 V: unknown	launched	ZYMAFLUOR 1MG COMPRIMIDOS	
KUWAIT	A: May 1979	launched	ZYMAFLUOR 1MG	
SRI LANKA	A: Jul 1980	launched	N/A	
BAHRAIN	A: Oct 1981 AR: Mar 1995	launched	ZYMAFLUOR 1MG	
ISRAEL	A: Dec 1982 AR: Nov 2002	none	ZYMAFLUOR 1MG	
COSTA RICA	A: Jul 1984 V: Jan 2001	launched	ZYMAFLUOR 1MG COMPRIMIDOS	
THAILAND	A: Aug 1985 AR: Sep 2003	launched	ZYMAFLUOR 1MG	
PERU	A: Sep 1986 AR: Dec 1991	launched	N/A	
SAUDI ARABIA	A: unknown V: unknown	launched	ZYMAFLUOR TABLETS 1MG	
GUATEMALA	A: Mar 1988 V: Oct 2002	launched	ZYMAFLUOR 1MG COMPRIMIDOS	

Country	Action date	Launch date	Trade name(s)	Comments
IVORY COAST	A: May 1989 V: unknown	none	N/A	
IRAQ	A: Jun 1989 V: unknown	launched	N/A	
EL SALVADOR	A: Jun 1989 V: unknown	launched	ZYMAFLUOR 1MG COMPRIMIDOS	
TAIWAN	A: Jul 1989 AR: Jul 2004	launched	ZYMAFLUOR 1MG	
D.R. CONGO	A: Oct 1989 AR: Feb 1994	launched	N/A	
CAMEROON	A: Oct 1989 AR: May 1991 V: unknown	launched	N/A	
LUXEMBURG	A: Mar 1990	none	N/A	
U. A. EMIRATES	A: Jun 1990 AR: Jun 1990 V: Feb 2008	launched	ZYMAFLUOR 1MG	
YEMEN	A: Dec 1990	launched	N/A	
UNITED KINGDOM	A: Jul 1991 AR: Dec 2005	none	ZYMAFLUOR TABLETS	
GERMANY	A: Aug 1991 AR: Jan 2005	launched	ZYMAFLUOR 1 MG//FLUORID 1MG	
QATAR	A: Feb 1992	launched	ZYMAFLUOR 1MG	
NICARAGUA	A: unknown AR: May 1983 V: Nov 2003	launched	ZYMAFLUOR 1MG COMPRIMIDOS	
TUNISIA	A: Jan 1994 AR: Dec 1997 V: Sep 2003	launched	ZYMAFLUOR 1MG COMPRIME	

Country	Action date	Launch date	Trade name(s)	Comments
ARGENTINA	A: Aug 1994 V: Aug 2004	launched	ZYMAFLUOR 1MG	
HUNGARY	A: Sep 1995 AR: Jan 2005 V: Jan 2006	launched	ZYMAFLUOR 1 MG TABLETTA	
HONDURAS	A: Feb 1996 V: unknown	launched	ZYMAFLUOR 1MG COMPRIMIDOS	
SPAIN	A: Mar 1997	none	ZYMAFLUOR 1 MG COMPRIMIDOS	
CZECH REPUBLIC	A: Jun 1997 V: Jun 2002	launched	N/A	
OMAN	A: Feb 1998	launched	ZYMAFLUOR 1MG	
POLAND	A: Jul 1998 AR: Sep 2003	launched	ZYMAFLUOR 1 MG	
TURKEY	A: Jan 2000	none	ZYMAFLUOR 1MG TABLET	
JORDAN	A: Jan 2000 V: Jan 2007	launched	ZYMAFLUOR TABBLET	
ROMANIA	A: Aug 2000 AR: Jun 2005	Aug 2000	ZYMAFLUOR 1MG	
BULGARIA	A: Apr 2001 AR: Feb 2006	launched	ZYMAFLUOR TABLET 1MG	
LAOS	A: Jan 2007	launched	ZYMAFLUOR 1 MG	
ALBANIA	A: unknown V: unknown	launched	ZYMAFLUOR 1MG	
JAMAICA	A: unknown	none	ZYMAFLUOR 1MG TABLETS	
CURACAO	A: unknown	launched	ZYMAFLUOR 1MG	

Country	Action date	Launch date	Trade name(s)	Comments
PORTUGAL	A: unknown AR: May 2005	launched	ZYMAFLUOR 1MG	
ARUBA	A: unknown V: unknown	launched	ZYMAFLUOR 1MG	
PARAGUAY	A: unknown AR: Jul 1989 V: unknown	launched	N/A	

DYNAVITAL FLUOR 0.5MG 1.105mg **Pharmaceutical Form:** capsule, hard

Country	Action date	Launch date	Trade name(s)	Comments
FRANCE	A: Dec 1988	none	DYNAVITAL FLUOR	

FLUREXAL NA FLUORIDE 10mg **Pharmaceutical Form:** gastro-resistant tablet

Country	Action date	Launch date	Trade name(s)	Comments
SWITZERLAND	A: Nov 1980 AR: Jul 1985	launched	N/A	
FRANCE	A: Apr 1984 AR: Apr 1994 V: Apr 1989	Jan 1985	RUMAFLUOR	
LEBANON	A: Jul 1988 V: unknown	launched	N/A	
GREECE	A: Sep 1989 AR: Jan 1998 V: unknown	Feb 1992	FLUREXIL	
PORTUGAL	A: Jun 1990 V: unknown	launched	N/A	
LUXEMBURG	A: Dec 1990 V: unknown	launched	N/A	
BELGIUM	A: Mar 1992 AR: Jul 2003	none	N/A	

ZYMAFLUOR NA FLUORIDE 0.25% **Pharmaceutical Form:** oral drops solution

Country	Action date	Launch date	Trade name(s)	Comments

Country	Action date	Launch date	Trade name(s)	Comments
SOUTH AFRICA	A: Jan 1992	launched	ZYMAFLUOR DROPS	
FRANCE	A: Aug 1992 AR: Mar 2002	Oct 1992	ZYMAFLUOR 0.114%	
SWITZERLAND	A: Mar 1994 AR: Mar 2004	none	ZYMAFLUOR GOUTTES	
BULGARIA	A: Nov 1994 AR: Apr 2002	launched	ZYMAFLUOR DROPS	
NETHERLANDS	A: Feb 1995 AR: Nov 1999	none	ZYMAFLUOR DRUPPELS	
PORTUGAL	A: Mar 1996 AR: May 2005	launched	ZYMAFLUOR	
TURKEY	A: Feb 1997	none	ZYMAFLUOR ORAL DAMLA	
SPAIN	A: Mar 1997 AR: Mar 2002	none	ZYMAFLUOR GOTAS	
POLAND	A: Jul 1998 AR: Sep 2003	launched	ZYMAFLUOR 0.114%	
PHILIPPINES	A: Sep 1998 V: unknown	launched	ZYMAFLUOR	
ITALY	A: Nov 1998 AR: May 2005	launched	ZYMAFLUOR GOCCE (1,14MG/ML ORAL DROPS, SOLUTION)	

A= authorized; AR= Authorization renewal; AQ= Authorized with qualifications; D= Divestment; LA= Lack of approval; V= voluntary marketing application withdrawal by company.

Appendix 3 - Line listings and summary tabulations

Appendix 3.1 Line listings HCP reports

Appendix 3.1.1 Serious spontaneous HCP reports

Appendix 3.1.2 Serious solicited suspected HCP reports

Appendix 3.1.3 Non-serious unlisted spontaneous HCP reports

Appendix 3.1.4 Non-serious listed spontaneous HCP reports

Appendix 3.2 Line listings non-HCP reports

Appendix 3.2.1 Serious spontaneous non-HCP reports

Appendix 3.2.2 Serious solicited suspected non-HCP reports

Appendix 3.2.3 Non-serious unlisted spontaneous non-HCP reports

Appendix 3.2.4 Non-serious listed spontaneous non-HCP reports

Appendix 3.3 Aggregate summary tabulations of reactions reported in PSUR period

Appendix 3.3.1 Aggregate summary tabulation HCP reports

Appendix 3.3.2 Aggregate summary tabulation non-HCP reports

Appendix 3.4 Cumulative summary tabulation of serious unlisted reactions

Aggregate summary tabulations of spontaneous and serious suspected solicited events reported in the PSUR period by MedDRA System Organ Class are presented in Appendix 3.3.1 for HCP reports and Appendix 3.3.2 for non-HCP reports. The tabulations show listedness and seriousness according to event level assessment as assessed at the time of receipt of the report. The tabulations show leading diagnoses, as well as signs and symptoms reported as related to the diagnoses. Related signs and symptoms will receive the same listedness assessment as the leading diagnosis to which they are related. From solicited reports, only the serious suspected reactions are presented in the summary tabulations (not-suspected events and/or non-serious events from serious suspected solicited reports are presented in the line listings but are not included in the summary tabulations).

Appendix 3.4.1 Cumulative summary tabulation HCP reports

Appendix 3.4.2 Cumulative summary tabulation non-HCP reports

Because for Zymafluor only case level assessment of seriousness and listedness (no event assessment) is available for legacy cases received prior to November 2002, a cumulative summary tabulation based on event level assessment cannot be provided. Therefore, a cumulative summary tabulation with preferred MedDRA terms for **all** events from all serious unlisted spontaneous reports and serious unlisted attributable clinical trial reports included in the safety database until data lock-point is presented in Appendix 3.4.1 for HCP reports and Appendix 3.4.2 for non-HCP reports. It should be noted that the cumulative summary tabulation includes all events reported in serious unlisted cases, regardless of whether the individual events were assessed as listed or unlisted, serious or non-serious. In addition, the tabulation includes all diagnoses as well as related signs and symptoms from individual serious unlisted reports.

There were 10 serious unlisted spontaneous reports and no serious unlisted attributable clinical trial reports until data lock point.

Period: 01-Apr-2006 Through 31-Jan-2009

Category: NCH PSURs + Add.

Sub Category:

Report Name: App 3.1.1 - Zymafluor [redacted] A

Agency Name: (No Specific Agency)

Header

Report# Line listing
Report Title App 3.1.1 - Zymafluor - Serious spontaneous HCP reports
☒ Ingredient SODIUM FLUORIDE
☐ Trade Name ZYMAFLUOR (NCH) (Unknown,), SODIUM FLUORIDE (NCH) (Solution,), ZYMAFLUOR (NCH) (Drops,), ZYMAFLUOR NA FLUORIDE (NCH) (Drops,), ZYMAFLUOR (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Unknown,), FLUREXAL (NCH) (Solution,), ZYMAFLUOR NA FLUORIDE (NCH) (Tablet,), ZYMAFLUOR NA FLUORIDE (NCH) (Unknown,), ZYMAFLUOR...

☐ IBD
Report Footer
☒ Print all configuration criteria on separate cover pages (PDF Only)
☐ Allow access to report cases through Hit List

Products

Ingredient: SODIUM FLUORIDE
Indication: (All Indications)
Formulation: (All Formulations)
ZYMAFLUOR H-T05480+TAB(Tablet,)
ZYMAFLUOR H-ZF+TAB(Tablet,)
ZYMAFLUOR H-ZF+SOL(Solution,)
ZYMAFLUOR H-ZF+(Unknown,)
ZYMAFLUOR H-ZF+DRP(Drops,)
FLUREXAL H-T05480+EFCTAB(Enteric-film-coated Tablet,)
ZYMAFLUOR H-T05480+(Unknown,)

Inclusion Criteria

Spontaneous Report ☒ Listed ☒ Unlisted ☒ Related ☒ Non-Related
☒ Serious ☐ Non-Serious Datasheet ☒ HCP ☐ Non-HCP
☒ Fatal ☒ Non-Fatal <ALL> ☐ Primary Reporter Only

Literature Case ☒ Listed ☒ Unlisted ☒ Related ☒ Non-Related
☒ Serious ☐ Non-Serious Datasheet ☒ HCP ☐ Non-HCP
☒ Fatal ☒ Non-Fatal <ALL> ☐ Primary Reporter Only

Listedness Assessment
◉ Use assessment in cases
○ Re-assess cases against datasheet in effect at beginning
○ Re-assess cases against datasheet in effect at end

Advanced Condition (None)

☐ Use Datasheet Assessment for UDF Tabulations

☐ Age Groups

☐ Adult (18-69 Y) ☐ Neonate (0-1 Y) ☐ Elderly (70-199 Y) ☐ Adolescent (13-17 Y)

☐ Infant (1-2 Y) ☐ Unborn (<0 Y) ☐ Child (3-12 Y) ☐ Unknown

Date Range

Case Creation Date		Case Receipt Date
From	01-APR-2006	From
To	31-JAN-2009	To

☐ Expeditable Only ☒ Exclude Follow-up Cases
☒ Include Unlocked Cases

☒ Include Line Listing Data Elements

☐ As Determined Causality	☐ As Determined Listedness	☐ As Reported Causality	☒ Case Abbreviated Narrative
☐ Case Central Safety Date	☐ Case Classification	☐ Case Comment Text	☐ Case Initial Receipt Date
☒ Case Listedness	☒ Case Narrative	☒ Case Number	☒ Case Outcome
☒ Case Report Type	☐ Case Seriousness?	☐ Clinical EUDRACT Number	☐ Clinical Study Reference
☐ Company Agent Causality?	☒ Country of Incidence	☐ Death Cause	☐ Death Cause HLGT
☐ Death Cause HLT	☐ Death Cause LLT	☐ Death Cause SOC	☐ Death Cause as Reported
☐ Dosage Regimen Batch / Lot #	☒ Dosage Regimen Daily Dose	☒ Dosage Regimen Duration	☒ Dosage Regimen Frequency
☒ Dosage Regimen Route of Administration	☒ Dosage Regimen Start Date/Time	☐ Drug Dechallenge?	☐ Drug Rechallenge?
☒ Event Description as Reported	☒ Event Onset Date/Time	☒ Event Preferred Term	☐ Lab Data - Tabular
☐ Literature Author	☒ Literature Journal	☐ Literature Pgs	☐ Literature Title
☐ Literature Vol	☐ Literature Year	☐ Outcome of Event	☒ Patient Age
☒ Patient Gender	☐ Patient Initials	☐ Patient Randomization Number	☒ Patient Relevant History
☐ Patient Sponsor Identifier	☐ Patient Subject #	☐ Product Indication Coding Status	☐ Product Indication HLGT
☐ Product Indication HLT	☐ Product Indication LLT	☐ Product Indication PT	☐ Product Indication SOC
☐ Product Indication as reported	☐ Product Indication to be coded	☒ Product Name	☐ Product Name Report Inclusion
☐ Report Comment	☐ Report Submission Date	☐ Reporter Type	☐ Study Center ID
☐ Study Drug	☐ Study ID	☐ Study Other ID	☐ Study Protocol ID

Options

Group By			
	Non Medically Confirmed	☒ Ascending	☒ Page Break
	Event System Organ Class	☒ Ascending	☐ Page Break
	Case Listedness	☒ Ascending	☐ Page Break

Sort By Case Number

MedDRA Hierarchy from ◉ Cases ○ Dictionary for Events

☐ Print Only the Term ◉ Preferred ○ Lower Level
☐ Print Dose Text in place of regimen dose
☐ Indicate if case was expedited Previously
☒ English Language ☐ Local Language --None--
☐ Place non-medically confirmed cases at the end
☐ Include non-serious listed cases in Line Listing at the end
☐ Print Event Info (Serious, Un-Listed, Causal) as Column
◉ List cases only once, under the primary event
○ List cases under all events, details under the primary event

☐ Print Product Indication for the Product selected in the Report

☐ Include Index of Cases in Report
☐ Include Line Listing Tabulation
☐ Include Initial Cases ☐ Include Follow-up Cases
☐ Include Summary of Cases Missing Assessments
☐ Include Summary of Unlocked Cases
☐ Include Cumulative Summary
☐ Print CIOMS Reports for Serious / Unlisted cases
☐ Domestic Consumer Report
☐ Adverse Event Summary
☐ Print Unsubmitted MedWatch Forms
☒ Include these summary tabulations / listings based on the set of cases presented in the line listing
* ER - Summary table
☐ Include these summary tabulations based on all cases
--None--
☐ Include these summary tabulations / listings based on the date range
--None--
* Exclude Follow-up Cases
☐ Additional Separate Page Numbering for UD Summaries

Ingredient: **SODIUM FLUORIDE**

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
Medically Confirmed (3)								
Event System Organ Class: Blood and lymphatic system disorders (1)								
Case Listedness: Unlisted (1)								
[redacted]	Spontaneous Report	8 Months Male	**ZYMAFLUOR (NCH) / Unknown** UNK [UNK]	Oral		04-OCT-2007 04-OCT-2007	Pancytopenia [PANCYTOPENIA] Myelogram revealed a global hypoplasia /Bone marrow hypoplasia [BONE MARROW FAILURE] - Thrombopenia [THROMBOCYTOPENIA] - Neutrophils were nearly absent [NEUTROPHIL COUNT ABNORMAL] - Major disorder of erytheopoiesis [ERYTHROPOIESIS ABNORMAL] Fever [PYREXIA] Cough [COUGH] Pallid [PALLOR]	Condition Unchanged

Product Name: ADVIL (IBUPROFEN) Suspect, Oral
DOLIPRANE (PARACETAMOL) Suspect, Rectal
HELICIDINE (HELICIDINE) Suspect, Oral

Case Listedness: Unlisted

Case Narrative: Initial report received on 02 Nov 2007 from a [redacted] A 8 month-old baby was treated with Zymafluor (sodium fluoride). The child experienced fever (38 C) and cough on 25 Sep 2007, during dental rise. The baby was treated with Doliprane (paracetamol) suppository and helicidine. On 29 Sep 2007 and on 01 Oct 2007, the baby was administered another suppository of Doliprane. On 01 Oct 2007, the baby was also administered Advil (ibuprofen) because the pain was persisting, due to dental rise, without fever. On 04 Oct 2007, the baby presented with fever at 39 C. Doliprane was administered again. The baby was pallid and was hospitalized. Pancytopenia was diagnosed (haemoglobin at 41g/l, platelets at 154 g/l, leukocytes at 3.1 g/l, neutrophils at 0.6 g/l, lymphocytes at 2.1 g/l). Myelogram revealed a global hypoplasia without blastic infiltrate, with major disorder of erythropoieisis and increase of young forms. The baby was administered blood transfusion and Tazocillin (piperacillin, tazobactam) and gentamycin which led to rapid decrease of fever. Two days later, thrombopenia was high (62 g/l) and there were no more neutrohils. Haemogobin was at 110 g/l since blood transfusion. On 10 Oct 2007, platelets were between 100 g/l and 120 g/l, neutrophils were nearly absent and haemoglobin decreased again to 83 g/l. On 11 Oct 2007 and on 18 Oct 2007, myelogram still revealed a persisting bone marrow hypoplasia with a development blockade at the promyelocyte step. At the time of the report, pancytopenia and marrow hypoplasia were still persisting. The [redacted] assessed the causality as [redacted] for Zymafluor, Advil, Doliprane and helicidine.

B

Event System Organ Class: Gastrointestinal disorders (1)								
Case Listedness: Unlisted (1)								
[redacted]	Spontaneous Report		**ZYMAFLUOR (NCH) / Unknown** UNK [UNK]	Oral			Dental fluorosis [FLUOROSIS DENTAL]	Unknown

Case Listedness: Unlisted

Case Narrative: Initial physician report received on 03 Oct 2007 with scanty information: This young patient experienced dental fluorosis while under treatment with Zymafluor (formulation and dosage unknown). Final outcome was unknown.

[2] Non-Medically Confirmed.

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
Event System Organ Class: Investigations (1)								
Case Listedness: Unlisted (1)								
[redacted]	Literature Case	Female	SODIUM FLUORIDE (NCH) / Unknown 25 mg [25 mg-QD]		1986 to 1988		Decreased bone mineral density [BONE DENSITY DECREASED]	Complete Recovery
						1990	Bone fracture/Recurrent, mutiple low or no impact fractures [FRACTURE]	
						1986	Osteoporosis [OSTEOPOROSIS]	
							Increased bone turnover [HIGH TURNOVER OSTEOPATHY]	
							A urine sample revealed an elevated level of fluoride during Teriparatide use [FLUORIDE INCREASED]	
						2006	Bone biospy showed disconnected network and sparse trabeculation [BIOPSY BONE ABNORMAL]	

Product Name: ALL OTHER THERAPEUTIC PRODUCTS (NO INGREDIENTS/SUBSTANCES) Suspect,
CALCIUM UNKNOWN (NCH) (CALCIUM) Suspect, Unknown,
CHOLECALCIFEROL (NCH) (CHOLECALCIFEROL) Suspect, Unknown,
IBANDRONIC ACID (IBANDRONIC ACID) Suspect,
TERIPARATIDE (TERIPARATIDE) Suspect,

Patient Relevant History: Current Condition; [redacted]norexia
Family History; [redacted]steoporosis
Current Condition; [redacted]menorrhoea

Literature Journal: Reactions 7 July 2007 2007; 28: 1159

Case Listedness: Unlisted

Case Narrative: This literature report was received on 10 Jul 2007: A female consumer with who had a history of anorexia, which resulted in amenorrhoea and a family history of osteoporosis, experienced decreased bone mineral density (BMD), recurrent fractures, and was diagnosed with osteoporosis in 1986 while receiving 25 mg SODIUM FLUORIDE (sodium fluoride) every day between 1986 and 1988 (exact dates unknown) for an unknown indication and during treatment with an unknown dose of TERIPARATIDE (teriparatide) for fluoride induced osteoporosis. In 1990, the consumer experienced her first fracture followed by multiple low or no impact fractures. Some of the fractures required internal fixation, bone grafting, and bone growth stimulator placement as treatment. Following SODIUM FLUORIDE (sodium fluoride) use, the bone mineral density test showed a very rapid increase in bone mineral density. In April 2003, dual energy x-ray absorptiometry (DXA) scan revealed total hip T-score of +0.4 and lumbar T-score of +3.0. Her osteoporosis medications were replaced with an unknown dose of TERIPARATIDE (teriparatide), CALCIUM UNKNOWN (calcium), and CHOLECALCIFEROL (cholecalciferol) and her bone turnover increased. However, approximately one year later, the bone mineral density tests revealed a large decrease at her lumbar spine and left hip. She experienced an additional fracture and the urine sample revealed an elevated level of SODIUM FLUORIDE (sodium fluoride) during TERIPARATIDE (teriparatide) use. In the spring of 2006, a magnetic resonance imagine based virtual bone biopsy showed a disconnected network and unusually sparse trabeculation. After completion of the 24-month TERIPARATIDE (teriparatide) therapy, she started to receive IBANDRONIC ACID (ibandronic acid). At 1-year follow-up, she had experienced no fractures and a dual energy x-ray absorptiometry scan showed stabilization of her bone mineral density. CONCLUSION: The author(s) commented that multiple peripheral fractures and high lumbar bone mineral density of T= +3 were associated with the previous sodium fluoride therapy and increased bone turnover due to a paradoxical decrease in the bone density and breakdown of the SODIUM FLUORIDE (sodium fluoride) containing bone tissue was associated with TERIPARATIDE (teriparatide) therapy.

Following internal review on 09 Oct 2007, Novartis comment was corrected.

Following internal review on 16 Oct 2007, the general tab was updated to reflect reporter as HCP "Health care profesional" field, "Yes" was selected.

Total number of case entries printed in the Medically Confirmed section: 3
Total number of cases printed in the Medically Confirmed section: 3
Total number of case entries printed: 3
Total number of cases printed: 3

[2] Non-Medically Confirmed.

B

Summary Tabulation

For All Products (Number of Events)

For the cases in this report

System Organ Class (SOC)	Preferred Term	Report Type: Literature Case	Spontaneous Report	**Total**
Blood and lymphatic system disorders	Bone marrow failure	0	1	**1**
	Erythropoiesis abnormal	0	1	**1**
	Pancytopenia	0	1	**1**
	Thrombocytopenia	0	1	**1**
	SubTotal	**0**	**4**	**4**
Gastrointestinal disorders	Fluorosis dental	0	1	**1**
	SubTotal	**0**	**1**	**1**
General disorders and administration site conditions	Pyrexia	0	1	**1**
	SubTotal	**0**	**1**	**1**
Injury, poisoning and procedural complications	Fracture	1	0	**1**
	SubTotal	**1**	**0**	**1**
Investigations	Biopsy bone abnormal	1	0	**1**
	Bone density decreased	1	0	**1**
	Fluoride increased	1	0	**1**
	Neutrophil count abnormal	0	1	**1**
	SubTotal	**3**	**1**	**4**

[2] Non-Medically Confirmed.

Summary Tabulation

For All Products (Number of Events)
For the cases in this report

System Organ Class (SOC)	Preferred Term	Report Type: Literature Case	Spontaneous Report	**Total**
Musculoskeletal and connective tissue disorders	High turnover osteopathy	1	0	**1**
	Osteoporosis	1	0	**1**
	SubTotal	**2**	**0**	**2**
Respiratory, thoracic and mediastinal disorders	Cough	0	1	**1**
	SubTotal	**0**	**1**	**1**
Vascular disorders	Pallor	0	1	**1**
	SubTotal	**0**	**1**	**1**
Total		**6**	**9**	**15**

[2] Non-Medically Confirmed.

Category: NCH PSURs + Add.

Sub Category:

Report Name: App 3.1.2 Zymafluor [redacted] A

Agency Name: (No Specific Agency)

Header

Report# Line listing
Report Title App 3.1.2 - Zymafluor - Serious solicited suspected HCP reports
☒ Ingredient SODIUM FLUORIDE
☐ Trade Name ZYMAFLUOR (NCH) (Unknown,), SODIUM FLUORIDE (NCH) (Solution,), ZYMAFLUOR (NCH) (Drops,), ZYMAFLUOR NA FLUORIDE (NCH) (Drops,), ZYMAFLUOR (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Unknown,), FLUREXAL (NCH) (Solution,), ZYMAFLUOR NA FLUORIDE (NCH) (Tablet,), ZYMAFLUOR NA FLUORIDE (NCH) (Unknown,), ZYMAFLUOR...
☐ IBD
Report Footer
☒ Print all configuration criteria on separate cover pages (PDF Only)
☐ Allow access to report cases through Hit List

Products

Ingredient: SODIUM FLUORIDE
Indication: (All Indications)
Formulation: (All Formulations)
ZYMAFLUOR H-T05480+TAB(Tablet,)
ZYMAFLUOR H-ZF+TAB(Tablet,)
ZYMAFLUOR H-ZF+SOL(Solution,)
ZYMAFLUOR H-ZF+(Unknown,)
ZYMAFLUOR H-ZF+DRP(Drops,)
FLUREXAL H-T05480+EFCTAB(Enteric-film-coated Tablet,)
ZYMAFLUOR H-T05480+(Unknown,)

Inclusion Criteria

Clinical Trial ☒ Listed ☒ Unlisted ☒ Related ☐ Non-Related
☒ Serious ☐ Non-Serious Datasheet ☒ HCP ☐ Non-HCP
☒ Fatal ☒ Non-Fatal <ALL> ☐ Primary Reporter Only

Listedness Assessment
- ◉ Use assessment in cases
- ○ Re-assess cases against datasheet in effect at beginning
- ○ Re-assess cases against datasheet in effect at end

Advanced Condition (None)

☐ Use Datasheet Assessment for UDF Tabulations

☐ **Age Groups**

☐ Adult (18-69 Y) ☐ Neonate (0-1 Y) ☐ Elderly (70-199 Y) ☐ Adolescent (13-17 Y)
☐ Infant (1-2 Y) ☐ Unborn (<0 Y) ☐ Child (3-12 Y) ☐ Unknown

Date Range

Case Creation Date		Case Receipt Date
From	01-APR-2006	From
To	31-JAN-2009	To

☐ Expeditable Only ☒ Exclude Follow-up Cases
☒ Include Unlocked Cases

☒ Include Line Listing Data Elements

☐ As Determined Causality	☐ As Determined Listedness	☐ As Reported Causality	☒ Case Abbreviated Narrative
☐ Case Central Safety Date	☐ Case Classification	☐ Case Comment Text	☐ Case Initial Receipt Date
☒ Case Listedness	☒ Case Narrative	☒ Case Number	☒ Case Outcome
☒ Case Report Type	☐ Case Seriousness?	☐ Clinical EUDRACT Number	☐ Clinical Study Reference
☐ Company Agent Causality?	☒ Country of Incidence	☐ Death Cause	☐ Death Cause HLGT
☐ Death Cause HLT	☐ Death Cause LLT	☐ Death Cause SOC	☐ Death Cause as Reported
☐ Dosage Regimen Batch / Lot #	☒ Dosage Regimen Daily Dose	☒ Dosage Regimen Duration	☒ Dosage Regimen Frequency
☒ Dosage Regimen Route of Administration	☒ Dosage Regimen Start Date/Time	☐ Drug Dechallenge?	☐ Drug Rechallenge?
☒ Event Description as Reported	☒ Event Onset Date/Time	☒ Event Preferred Term	☐ Lab Data - Tabular
☐ Literature Author	☒ Literature Journal	☐ Literature Pgs	☐ Literature Title
☐ Literature Vol	☐ Literature Year	☐ Outcome of Event	☒ Patient Age
☒ Patient Gender	☐ Patient Initials	☐ Patient Randomization Number	☒ Patient Relevant History
☐ Patient Sponsor Identifier	☐ Patient Subject #	☐ Product Indication Coding Status	☐ Product Indication HLGT
☐ Product Indication HLT	☐ Product Indication LLT	☐ Product Indication PT	☐ Product Indication SOC
☐ Product Indication as reported	☐ Product Indication to be coded	☒ Product Name	☐ Product Name Report Inclusion
☐ Report Comment	☐ Report Submission Date	☐ Reporter Type	☐ Study Center ID
☐ Study Drug	☐ Study ID	☐ Study Other ID	☐ Study Protocol ID

Options

Group By			
	Non Medically Confirmed	☒ Ascending	☒ Page Break
	Event System Organ Class	☒ Ascending	☐ Page Break
	Case Listedness	☒ Ascending	☐ Page Break

Sort By Case Number
MedDRA Hierarchy from ◉ Cases ○ Dictionary for Events
☐ Print Only the Term ◉ Preferred ○ Lower Level
☐ Print Dose Text in place of regimen dose
☐ Indicate if case was expedited Previously
☒ English Language ☐ Local Language --None--

☐ Place non-medically confirmed cases at the end
☐ Include non-serious listed cases in Line Listing at the end
☐ Print Event Info (Serious, Un-Listed, Causal) as Column
◉ List cases only once, under the primary event
○ List cases under all events, details under the primary event

☐ Print Product Indication for the Product selected in the Report

☐ Include Index of Cases in Report
☐ Include Line Listing Tabulation
☐ Include Initial Cases ☐ Include Follow-up Cases
☐ Include Summary of Cases Missing Assessments
☐ Include Summary of Unlocked Cases
☐ Include Cumulative Summary
☐ Print CIOMS Reports for Serious / Unlisted cases
☐ Domestic Consumer Report
☐ Adverse Event Summary
☐ Print Unsubmitted MedWatch Forms
☒ Include these summary tabulations / listings based on the set of cases presented in the line listing
* ER - Summary table
☐ Include these summary tabulations based on all cases
--None--
☐ Include these summary tabulations / listings based on the date range
--None--
* Exclude Follow-up Cases
☐ Additional Separate Page Numbering for UD Summaries

Period: 01-Apr-2006 Through 31-Jan-2009

Ingredient: SODIUM FLUORIDE

Case Number	Country Source	Age Sex	Daily Dose [Dose Frequency]	Form / Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome

No Data Found

[2] Non-Medically Confirmed. [3] Unlocked Case.

Period: 01-Apr-2006 Through 31-Jan-2009

Category: NCH PSURs + Add.

Sub Category:

Report Name: App 3.1.3-Zymafluor [redacted]

A

Agency Name: (No Specific Agency)

Header

Report# Line listing

Report Title App 3.1.3 - Zymafluor - Non-serious unlisted spontaneous HCP reports

☒ Ingredient SODIUM FLUORIDE

☐ Trade Name ZYMAFLUOR (NCH) (Unknown,), SODIUM FLUORIDE (NCH) (Solution,), ZYMAFLUOR (NCH) (Drops,), ZYMAFLUOR NA FLUORIDE (NCH) (Drops,), SODIUM FLUORIDE (NCH) (Unknown,), FLUREXAL (NCH) (Solution,), ZYMAFLUOR NA FLUORIDE (NCH) (Tablet,), ZYMAFLUOR NA FLUORIDE (NCH) (Unknown,), ZYMAFLUOR (NCH) (Solution,), ZYMAFLUOR NA FLUORIDE (NCH) (Solution,), SODIUM FLUORIDE(NCH) (Solution,), FLU...

☐ IBD

Report Footer

☒ Print all configuration criteria on separate cover pages (PDF Only)

☐ Allow access to report cases through Hit List

Products

Ingredient: SODIUM FLUORIDE

Indication: (All Indications)

Formulation: (All Formulations)

ZYMAFLUOR H-ZF+TAB(Tablet,)

ZYMAFLUOR H-T05480+TAB(Tablet,)

ZYMAFLUOR H-ZF+SOL(Solution,)

ZYMAFLUOR H-ZF+(Unknown,)

ZYMAFLUOR H-ZF+DRP(Drops,)

ZYMAFLUOR H-T05480+(Unknown,)

Inclusion Criteria

Literature Case ☐ Listed ☒ Unlisted ☒ Related ☒ Non-Related

☐ Serious ☒ Non-Serious Datasheet ☒ HCP ☐ Non-HCP

☐ Fatal ☒ Non-Fatal <ALL> ☐ Primary Reporter Only

Spontaneous Report ☐ Listed ☒ Unlisted ☒ Related ☒ Non-Related

☐ Serious ☒ Non-Serious Datasheet ☒ HCP ☐ Non-HCP

☐ Fatal ☒ Non-Fatal <ALL> ☐ Primary Reporter Only

Listedness Assessment

◉ Use assessment in cases

○ Re-assess cases against datasheet in effect at beginning

○ Re-assess cases against datasheet in effect at end

Advanced Condition nch_psur_nonserious_unlisted_hcp

☐ Use Datasheet Assessment for UDF Tabulations

☐ Age Groups

☐ Adult (18-69 Y) ☐ Neonate (0-1 Y) ☐ Elderly (70-199 Y) ☐ Adolescent (13-17 Y)
☐ Infant (1-2 Y) ☐ Unborn (<0 Y) ☐ Child (3-12 Y) ☐ Unknown

Date Range

Case Creation Date		Case Receipt Date
From	01-APR-2006	From
To	31-JAN-2009	To

☐ Expeditable Only ☒ Exclude Follow-up Cases
☒ Include Unlocked Cases

☒ Include Line Listing Data Elements

☐ As Determined Causality	☐ As Determined Listedness	☐ As Reported Causality	☒ Case Abbreviated Narrative
☐ Case Central Safety Date	☐ Case Classification	☐ Case Comment Text	☐ Case Initial Receipt Date
☐ Case Listedness	☒ Case Narrative	☒ Case Number	☒ Case Outcome
☒ Case Report Type	☐ Case Seriousness?	☐ Clinical EUDRACT Number	☐ Clinical Study Reference
☐ Company Agent Causality?	☒ Country of Incidence	☐ Death Cause	☐ Death Cause HLGT
☐ Death Cause HLT	☐ Death Cause LLT	☐ Death Cause SOC	☐ Death Cause as Reported
☐ Dosage Regimen Batch / Lot #	☒ Dosage Regimen Daily Dose	☒ Dosage Regimen Duration	☒ Dosage Regimen Frequency
☒ Dosage Regimen Route of Administration	☒ Dosage Regimen Start Date/Time	☐ Drug Dechallenge?	☐ Drug Rechallenge?
☒ Event Description as Reported	☒ Event Onset Date/Time	☒ Event Preferred Term	☐ Lab Data - Tabular
☐ Literature Author	☒ Literature Journal	☐ Literature Pgs	☐ Literature Title
☐ Literature Vol	☐ Literature Year	☐ Outcome of Event	☒ Patient Age
☒ Patient Gender	☐ Patient Initials	☐ Patient Randomization Number	☒ Patient Relevant History
☐ Patient Sponsor Identifier	☐ Patient Subject #	☐ Product Indication Coding Status	☐ Product Indication HLGT
☐ Product Indication HLT	☐ Product Indication LLT	☐ Product Indication PT	☐ Product Indication SOC
☐ Product Indication as reported	☐ Product Indication to be coded	☒ Product Name	☐ Product Name Report Inclusion
☐ Report Comment	☐ Report Submission Date	☐ Reporter Type	☐ Study Center ID
☐ Study Drug	☐ Study ID	☐ Study Other ID	☐ Study Protocol ID

Options

Group By			
	Non Medically Confirmed	☒ Ascending	☒ Page Break
	Event System Organ Class	☒ Ascending	☐ Page Break

Sort By Case Number
MedDRA Hierarchy from ◉ Cases ○ Dictionary for Events
☐ Print Only the Term ◉ Preferred ○ Lower Level

- ☐ Print Dose Text in place of regimen dose
- ☐ Indicate if case was expedited Previously
- ☒ English Language ☐ Local Language --None--
- ☐ Place non-medically confirmed cases at the end
- ☐ Include non-serious listed cases in Line Listing at the end
- ☐ Print Event Info (Serious, Un-Listed, Causal) as Column
- ◉ List cases only once, under the primary event
- ○ List cases under all events, details under the primary event

- ☐ Print Product Indication for the Product selected in the Report

- ☐ Include Index of Cases in Report
- ☐ Include Line Listing Tabulation
  - ☐ Include Initial Cases ☐ Include Follow-up Cases
- ☐ Include Summary of Cases Missing Assessments
- ☐ Include Summary of Unlocked Cases
- ☐ Include Cumulative Summary
- ☐ Print CIOMS Reports for Serious / Unlisted cases
- ☐ Domestic Consumer Report
- ☐ Adverse Event Summary
- ☐ Print Unsubmitted MedWatch Forms
- ☒ Include these summary tabulations / listings based on the set of cases presented in the line listing
  * ER - Summary table
- ☐ Include these summary tabulations based on all cases
  --None--
- ☐ Include these summary tabulations / listings based on the date range
  --None--

* Exclude Follow-up Cases

- ☐ Additional Separate Page Numbering for UD Summaries

Advanced Condition used in this report:

Advanced Condition: nch_psur_nonserious_unlisted_hcp (Created by [redacted] C
Selection Criteria:
Advanced Condition nch_psur_nonserious_unlisted_hcp is overwritten by the following SQL statement:
SELECT DISTINCT cm.case_id FROM case_master cm, case_product cp, case_assess ca, (SELECT DISTINCT case_id, MAX(Hcp_Flag) Hcp_flag FROM case_reporters GROUP BY case_id) cr WHERE cm.case_id = cp.case_id AND cm.case_id = cr.case_id AND CR.hcp_flag = 1 AND cm.case_id = ca.case_id (+)
AND (UPPER(cp.co_drug_code) like 'H-ZF+%' OR UPPER(cp.co_drug_code) like 'H-T05480+%'

) AND cp.drug_type = 1 AND cm.state_id > 1 AND cm.rpt_type_id IN (1,3) AND ca.SERIOUSNESS = 0 AND ca.listedness = 2
AND (TRUNC(cm.create_time) between TO_DATE('01-Apr-2006', 'DD-MON-YYYY') and TO_DATE('31-Jan-2009', 'DD-MON-YYYY')) AND cm.case_id NOT IN (SELECT case_id FROM case_classifications WHERE classification_id IN ([redacted]
B

Period: 01-Apr-2006 Through 31-Jan-2009

Ingredient: SODIUM FLUORIDE

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
Medically Confirmed (15)								
Event System Organ Class: Gastrointestinal disorders (9)								
[redacted]	Spontaneous Report	2 Years Female	ZYMAFLUOR (NCH) / Unknown UNK [ONCE/SINGLE]	Oral	01-OCT-2006 to 01-OCT-2006	01-OCT-2006 01-OCT-2006	Orange yellow colored tongue [TONGUE DISCOLOURATION] 2 year old girl ingested half a bottle of Zymafluor [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
	Case Narrative:	Report received from a physician on 04 Oct 2006: A 2 year old girl ingested half a bottle of Zymafluor 0,114% (sodium fluoride) on 01 Oct 2006. The reporting physician was consulted 4 days later. The examination only revealed an orange yellow colored tongue. The little girl was quite well; she was asymptomatic after ingestion. Zymafluor was discontinued on 04 Oct 2006. No special measure was required. Outcome: complete recovery. Follow-up data received on 13 Nov 2006: The reporting physician specified that the baby was treated with Zymaduo from birth and that the orange colouration of the tongue persisted for 3 weeks. No other symptom was observed. At the time of the report, the baby recovered.						
[redacted]	Spontaneous Report	7 Years	ZYMAFLUOR (NCH) / Unknown UNK [UNK]	Oral	2004 to Unknown	23-JAN-2008	Brownish teeth mottling [TOOTH DISCOLOURATION]	Condition Unchanged
	Product Name:	ZYMAFLUOR D (NCH) (SODIUM FLUORIDE, CHOLECALCIFEROL) Suspect, Unknown, Oral						
[redacted]	Spontaneous Report		ZYMAFLUOR (NCH) / Unknown UNK [UNK]	Oral			Yellowish coating on the teeth which could be scratched off [TOOTH DISCOLOURATION]	Unknown
	Case Narrative:	Initial pharmacist report received on 09 May 2008: a child used Zymafluor 0.5 mg (sodium fluoride) and developed yellowish coating on the teeth which could be scratched off. Zymafluor was continued. Outcome: unknown. (see related case [redacted]						
[redacted]	Spontaneous Report		ZYMAFLUOR (NCH) / Unknown UNK [UNK]	Oral			Yellowish coating on the teeth which could be scratched off [TOOTH DISCOLOURATION]	Unknown
	Case Narrative:	Initial pharmacist report received on 09 May 2008: a child used Zymafluor 0.5 mg (sodium fluoride) and developed yellowish coating on the teeth which could be scratched off. Zymafluor was continued. Outcome: unknown. (see related case [redacted]						
[redacted]	Spontaneous Report	3 Weeks Male	ZYMAFLUOR (NCH) / Unknown UNK [UNK]	Oral	23-OCT-2008 to 26-OCT-2008	23-OCT-2008 23-OCT-2008	Flatulence [FLATULENCE] Restlessness [RESTLESSNESS]	Complete Recovery
[redacted]	Spontaneous Report	13 Months Male	ZYMAFLUOR (NCH) / Drops 4 drp [4 drp-QD]	Oral	27-JAN-2008 to 29-JAN-2008	27-JAN-2008 27-JAN-2008 27-JAN-2008	Bloating and erythema in the oral cavity [OEDEMA MOUTH] Oedema of mucosa [OEDEMA MUCOSAL] Erythema in the oral cavity [PHARYNGEAL ERYTHEMA]	Condition Improving
[redacted]	Spontaneous Report	6 Years Female	ZYMAFLUOR (NCH) / Unknown UNK [UNK]	Oral			Fluorosis in upper lateral left incisor and lower right incisor [FLUOROSIS DENTAL] - 2 eruptive teeth presented pigmentation signs / whitish opaque blotches [TOOTH DISCOLOURATION]	Not Reported
	Patient Relevant History:	Current Condition; ([redacted] Autism						

[2] Non-Medically Confirmed.

Period: 01-Apr-2006 Through 31-Jan-2009

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
[redacted]	Spontaneous Report	6 Months Male	**ZYMAFLUOR (NCH) / Unknown** UNK [UNK]	Oral	27-FEB-2008 to 02-MAR-2008	01-MAR-2008	Stomatitis [STOMATITIS]	Not Reported
		Product Name:	VITAMIN D (ERGOCALCIFEROL) Concom, VITAMIN K (PHYTOMENADIONE) Concom,					
		Case Narrative:	Initial report received from physician via [redacted] on 18 Apr 2008. This child was treated with Zymafluor (sodium fluoride) since 27 Feb 2008 for fluoroprophylaxis. On 01 Mar 2008, the child experienced stomatitis. Zymafluor treatment was discontinued on 02 Mar 2008. Ambulatory treatment was required. Final outcome was not reported.					
[redacted]	Spontaneous Report	2 Years Female	**ZYMAFLUOR (NCH) / Unknown** .25 mg [.25 mg-QD]	Oral	JAN-2008 Ongoing	SEP-2008	Acute gastritis [GASTRITIS]	Complete Recovery
						06-SEP-2008	Colic [ABDOMINAL PAIN]	
						06-SEP-2008	Diarrhea [DIARRHOEA]	
			UNK [UNK]	Oral	06-SEP-2008 to Unknown	06-SEP-2008	Fever [PYREXIA]	
						06-SEP-2008	Child took several tablets at the same time [ACCIDENTAL DRUG INTAKE BY CHILD]	
							Child took several tablets [ACCIDENTAL OVERDOSE]	
		Case Narrative:	Initial report received by a pharmacist who was also the patient's grand-mother. This 2-year-old child was administered one tablet of Zymafluor 1mg (sodium fluoride) per day since Jan 2008 as prescribed by a physician. On 06 Sep 2008 the child took several tablets at the same time (number unknown). During that night the child experienced colic, diarrhea and fever. As the events continued for four days, a physician was consulted and said that the reaction was not related to Zymafluor and was probably due to an acute gastritis. At the date of this report the treatment with Zymafluor 1mg was ongoing and the final outcome was complete recovery. Internal review of the initial data received on 18 Sep 2009 was done on 27 Feb 2009: the child was prescribed Zymalfuor 0.25 mg and not Zymalfuor 1 mg as previously reported. The event "accidental overdose" was added. No other information was changed. Follow-up information was requested					
Event System Organ Class: General disorders and administration site conditions (2)								
[redacted]	Spontaneous Report	3 Years Male	**ZYMAFLUOR (NCH) / Tablet** 80 DF [80 DF-ONCE/SINGLE]	Oral	OCT-2006 to OCT-2006	25-OCT-2006	Feeling sick [MALAISE]	Not Applicable
						25-OCT-2006	Bad taste [DYSGEUSIA]	
						25-OCT-2006	He cried [CRYING]	
						25-OCT-2006	Gastric pain [ABDOMINAL PAIN UPPER]	
						25-OCT-2006	Symptomatic acute ingestion of around 80 tablets [ACCIDENTAL DRUG INTAKE BY CHILD]	
							Ingested around 80 Zymafluor [ACCIDENTAL OVERDOSE]	
		Case Narrative:	Reported received on 25 Oct 2006 by a pharmacist: The 3 year old patient ingested around 80 Zymafluor 0,5 mg tablets (sodium fluoride) around 16:00 (i.e. 40 mg for 16 kg, or 2,5 mg/kg). The child complained of gastric pain, feeling sick, bad taste and he cried. He did not experience any other symptom. The treatment with Zymafluor was discontinued for 15 days. The child was to be given milky products in order to bring a calcium intake. He was to be followed up, notably for the onset of vomiting that should require to consult at hospital. The outcome was unknown. Follow-up information received on 08 Nov 2006 from pharmacist: The reporting pharmacist confirmed the nature of the events and stated that they lasted for 3 hours. The total amount of tablets ingested by the child on 25 Oct 2006 was 80 tablets of Zymafluor 0.5 mg. The symptomatic treatment was made of milky products and the child recovered. Zymafluor was stopped and not restarted. Follow-up information received on 22 Nov 2006 from pharmacist: The reporting pharmacist specified that the consulted practitioner only informed the mother that this event was not significant prior to discharging her. The child was not hospitalized and no special plasma assay was performed.					

[2] Non-Medically Confirmed.

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
[redacted]	Spontaneous Report	24 Months Female	ZYMAFLUOR (NCH) / Unknown .25 mg [.25 mg-QD]	Oral	JUL-2006 to NOV-2006		Slight inflammatory reaction [INFLAMMATION]	Not Reported
							Probably starting calcification [CALCINOSIS]	
						DEC-2006	Hyperkeratotics nails of the third right toe with distal detachment [HYPERKERATOSIS]	
			.5 mg [.5 mg-QD]	Oral	NOV-2006 Ongoing			
						DEC-2006	Dystrophy of the feet nails [NAIL DYSTROPHY]	
						DEC-2006	Nails appeared thickened with a yellow/brown coloration [NAIL DISORDER]	
						DEC-2006	Nails appeared thickened with a yellow/brown coloration. [NAIL DISCOLOURATION]	

Case Narrative: Initial physician report received on 28 Feb 2007: The infant experienced dystrophy of the feet nails while on treatment with Zymafluor (sodium fluoride). The nails appeared thickened with a yellow / brown coloration. Product was taken for caries prevention. It was unknown whether the product was continued. The outcome of the events were not reported.

Follow-up information received from a physician on 21 Mar 2007. The physician stated that a dystrophy of some nails appeared in Dec 2006 as yellow-coloured and hyperkeratosis was observed on the nail of the third right toe, with distal detachment. The treatment was continued and the lesions remained unchanged. A mycological exam was negative but confirmed an intense microscopic nail dystrophy with a slight inflammatory reaction and probable starting calcifications. The outcome was reported as reaction continues.

Event System Organ Class: Musculoskeletal and connective tissue disorders (1)

[redacted]	Spontaneous Report	54 Years Female	ZYMAFLUOR (NCH) / Unknown UNK [UNK]	Oral			Osteoporosis [OSTEOPOROSIS]	Not Reported

Event System Organ Class: Nervous system disorders (1)

[redacted]	Spontaneous Report	Years Male	ZYMAFLUOR (NCH) / Tablet .25 mg [.25 mg-QD]	Oral			Trembling [TREMOR]	Complete Recovery
							Howling [CRYING]	
							Nervousness [NERVOUSNESS]	

Product Name: D-FLUORETTEN (CHOLESTEROL, COLECALCIFEROL, SODIUM FLUORIDE) Suspect, Tablet, daily dose: 1DF, dose: 1DF, QD, Oral

Event System Organ Class: Skin and subcutaneous tissue disorders (2)

[redacted]	Spontaneous Report	16 Months Male	ZYMAFLUOR (NCH) / Unknown UNK [.25 mg-UNK]	Oral	Unknown to MAY-2006	MAY-2006	Sweating increased at the trunk [HYPERHIDROSIS]	Complete Recovery
						MAY-2006	"Child turned pale" [PALLOR]	
						MAY-2006	*- Child got "rings under his eyes" [DARK CIRCLES UNDER EYES]*	

Case Narrative: This case combines initial information received on 05 Jul 2006 and follow-up information received on 06 Jul 2006 from a pharmacist: The patient was treated with Zymafluor 0.25 mg (sodium fluoride). In May 2006, the mother of this child noticed that her child developed an increased sweating at the trunk approximately 30 to 45 minutes after each intake of Zymafluor 0.25 mg. Additionally, her child "turned pale" and the mother had the impression that her child "got rings under his eyes". The consulted children's specialist did not find any pathological symptoms and stated that the child was completely normal. Zymaflour 0.25 mg was stopped by the mother. The patient recovered.

[redacted]	Spontaneous Report	11 Years Male	ZYMAFLUOR (NCH) / Unknown 1 mg [1 mg-QD]	Oral	12-JUN-2007 to 10-AUG-2007	JUL-2007	Hair loss [ALOPECIA]	Complete Recovery
							Stress [STRESS]	
							Unspecified vitamin deficiency [HYPOVITAMINOSIS]	

Patient Relevant History: Current Condition; (10003553); Asthma
Note: allergic asthma
Current Condition; (10013786); Dry skin
Note: with scaling
Current Condition; (10012438); Dermatitis atopic

Product Name: CINKORAT () Concom,
DACAKUNA () Concom,

[2] Non-Medically Confirmed.

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
		Case Narrative:	This physician report combines initial information received on 20 Aug 2007 and follow-up information received on 31 Aug 2007. This 11 year-old child started Zymafluor (sodium fluoride) on 12 Jun 2007. In Jul 2007, the child experienced hair loss. Zymafluor was discontinued on 10 Aug 2007. Adverse symptoms lasted all together for about 1 month. The reporting physician stated that the causality rating of the pharmacist and the treating family doctor was "not related". The pharmacist presumed that stress or an unspecified vitamin deficiency as possible cause of the reaction. Final outcome: completely recovered. Follow-up report received on 21 Sep 2007 from a physician: The reporting physician confirmed the initially reported reaction and specified that the child developed increased hair loss of all dark hair after intake of Zymafluor 1 mg. Zymafluor was stopped. Final outcome: completely recovered.			

Total number of case entries printed in the Medically Confirmed section: 15
Total number of cases printed in the Medically Confirmed section: 15
Total number of case entries printed: 15
Total number of cases printed: 15

[2] Non-Medically Confirmed.

Summary Tabulation

For All Products (Number of Events)

For the cases in this report

System Organ Class (SOC)	Preferred Term	Report Type: Spontaneous Report	Total
Eye disorders	Dark circles under eyes	1	**1**
	SubTotal	**1**	**1**
Gastrointestinal disorders	Abdominal pain	1	**1**
	Abdominal pain upper	1	**1**
	Diarrhoea	1	**1**
	Flatulence	1	**1**
	Fluorosis dental	1	**1**
	Gastritis	1	**1**
	Oedema mouth	1	**1**
	Stomatitis	1	**1**
	Tongue discolouration	1	**1**
	Tooth discolouration	4	**4**
	SubTotal	**13**	**13**
General disorders and administration site conditions	Calcinosis	1	**1**
	Inflammation	1	**1**
	Malaise	1	**1**
	Oedema mucosal	1	**1**
	Pyrexia	1	**1**
	SubTotal	**5**	**5**

[2] Non-Medically Confirmed.

Summary Tabulation

For All Products (Number of Events)

For the cases in this report

System Organ Class (SOC)	Preferred Term	Report Type: Spontaneous Report	Total
Injury, poisoning and procedural complications	Accidental drug intake by child	3	**3**
	Accidental overdose	2	**2**
	SubTotal	**5**	**5**
Metabolism and nutrition disorders	Hypovitaminosis	1	**1**
	SubTotal	**1**	**1**
Musculoskeletal and connective tissue disorders	Osteoporosis	1	**1**
	SubTotal	**1**	**1**
Nervous system disorders	Dysgeusia	1	**1**
	Tremor	1	**1**
	SubTotal	**2**	**2**
Psychiatric disorders	Crying	2	**2**
	Nervousness	1	**1**
	Restlessness	1	**1**
	Stress	1	**1**
	SubTotal	**5**	**5**
Respiratory, thoracic and mediastinal disorders	Pharyngeal erythema	1	**1**
	SubTotal	**1**	**1**

[2] Non-Medically Confirmed.

Summary Tabulation

For All Products (Number of Events)

For the cases in this report

System Organ Class (SOC)	Preferred Term	Report Type: Spontaneous Report	Total
Skin and subcutaneous tissue disorders	Alopecia	1	**1**
	Hyperhidrosis	1	**1**
	Hyperkeratosis	1	**1**
	Nail discolouration	1	**1**
	Nail disorder	1	**1**
	Nail dystrophy	1	**1**
	SubTotal	**6**	**6**
Vascular disorders	Pallor	1	**1**
	SubTotal	**1**	**1**
Total		**41**	**41**

[2] Non-Medically Confirmed.

Period: 01-Apr-2006 Through 31-Jan-2009

Category: NCH PSURs + Add.

Sub Category:

Report Name: App 3.1.4-Zymafluor[redacted] A

Agency Name: (No Specific Agency)

Header

Report# Line listing
Report Title App 3.1.4 - Zymafluor - Non-serious listed spontaneous HCP reports
☒ Ingredient SODIUM FLUORIDE
☐ Trade Name ZYMAFLUOR (NCH) (Unknown,), SODIUM FLUORIDE (NCH) (Solution,), ZYMAFLUOR (NCH) (Drops,), ZYMAFLUOR NA FLUORIDE (NCH) (Drops,), ZYMAFLUOR (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Unknown,), FLUREXAL (NCH) (Solution,), ZYMAFLUOR NA FLUORIDE (NCH) (Tablet,), ZYMAFLUOR NA FLUORIDE (NCH) (Unknown,), ZYMAFLUOR...
☐ IBD
Report Footer
☒ Print all configuration criteria on separate cover pages (PDF Only)
☐ Allow access to report cases through Hit List

Products

Ingredient: SODIUM FLUORIDE
Indication: (All Indications)
Formulation: (All Formulations)
ZYMAFLUOR H-T05480+TAB(Tablet,)
ZYMAFLUOR H-ZF+TAB(Tablet,)
ZYMAFLUOR H-ZF+SOL(Solution,)
ZYMAFLUOR H-ZF+(Unknown,)
ZYMAFLUOR H-ZF+DRP(Drops,)
FLUREXAL H-T05480+EFCTAB(Enteric-film-coated Tablet,)
ZYMAFLUOR H-T05480+(Unknown,)

Inclusion Criteria

Spontaneous Report ☒ *Listed* ☐ *Unlisted* ☒ *Related* ☒ *Non-Related*
☐ Serious ☒ Non-Serious Datasheet ☒ HCP ☐ Non-HCP
☐ Fatal ☒ Non-Fatal <ALL> ☐ Primary Reporter Only

Literature Case ☒ Listed ☐ Unlisted ☒ Related ☒ Non-Related
☐ Serious ☒ Non-Serious Datasheet ☒ HCP ☐ Non-HCP
☐ Fatal ☒ Non-Fatal <ALL> ☐ Primary Reporter Only

Listedness Assessment
◉ Use assessment in cases
○ Re-assess cases against datasheet in effect at beginning
○ Re-assess cases against datasheet in effect at end

Advanced Condition nch_psur_nonserious_listed_hcp

☐ Use Datasheet Assessment for UDF Tabulations

☐ Age Groups

☐ Adult (18-69 Y) ☐ Neonate (0-1 Y) ☐ Elderly (70-199 Y) ☐ Adolescent (13-17 Y)

☐ Infant (1-2 Y) ☐ Unborn (<0 Y) ☐ Child (3-12 Y) ☐ Unknown

Date Range

Case Creation Date		Case Receipt Date
From	01-APR-2006	From
To	31-JAN-2009	To

☐ Expediteable Only ☒ Exclude Follow-up Cases
☒ Include Unlocked Cases

☒ Include Line Listing Data Elements

☐ As Determined Causality	☐ As Determined Listedness	☐ As Reported Causality	☒ Case Abbreviated Narrative
☐ Case Central Safety Date	☐ Case Classification	☐ Case Comment Text	☐ Case Initial Receipt Date
☐ Case Listedness	☒ Case Narrative	☒ Case Number	☒ Case Outcome
☒ Case Report Type	☐ Case Seriousness?	☐ Clinical EUDRACT Number	☐ Clinical Study Reference
☐ Company Agent Causality?	☒ Country of Incidence	☐ Death Cause	☐ Death Cause HLGT
☐ Death Cause HLT	☐ Death Cause LLT	☐ Death Cause SOC	☐ Death Cause as Reported
☐ Dosage Regimen Batch / Lot #	☒ Dosage Regimen Daily Dose	☒ Dosage Regimen Duration	☒ Dosage Regimen Frequency
☒ Dosage Regimen Route of Administration	☒ Dosage Regimen Start Date/Time	☐ Drug Dechallenge?	☐ Drug Rechallenge?
☒ Event Description as Reported	☒ Event Onset Date/Time	☒ Event Preferred Term	☐ Lab Data - Tabular
☐ Literature Author	☒ Literature Journal	☐ Literature Pgs	☐ Literature Title
☐ Literature Vol	☐ Literature Year	☐ Outcome of Event	☒ Patient Age
☒ Patient Gender	☐ Patient Initials	☐ Patient Randomization Number	☒ Patient Relevant History
☐ Patient Sponsor Identifier	☐ Patient Subject #	☐ Product Indication Coding Status	☐ Product Indication HLGT
☐ Product Indication HLT	☐ Product Indication LLT	☐ Product Indication PT	☐ Product Indication SOC
☐ Product Indication as reported	☐ Product Indication to be coded	☒ Product Name	☐ Product Name Report Inclusion
☐ Report Comment	☐ Report Submission Date	☐ Reporter Type	☐ Study Center ID
☐ Study Drug	☐ Study ID	☐ Study Other ID	☐ Study Protocol ID

Options

Group By			
	Non Medically Confirmed	☒ Ascending	☒ Page Break
	Event System Organ Class	☒ Ascending	☐ Page Break

Sort By Case Number

MedDRA Hierarchy from ◉ Cases ○ Dictionary for Events

☐ Print Only the Term ◉ Preferred ○ Lower Level

☐ Print Dose Text in place of regimen dose
☐ Indicate if case was expedited Previously
☒ English Language ☐ Local Language –None–
☐ Place non-medically confirmed cases at the end
☐ Include non-serious listed cases in Line Listing at the end
☐ Print Event Info (Serious, Un-Listed, Causal) as Column
◉ List cases only once, under the primary event
○ List cases under all events, details under the primary event

☐ Print Product Indication for the Product selected in the Report

☐ Include Index of Cases in Report
☐ Include Line Listing Tabulation
☐ Include Initial Cases ☐ Include Follow-up Cases
☐ Include Summary of Cases Missing Assessments
☐ Include Summary of Unlocked Cases
☐ Include Cumulative Summary
☐ Print CIOMS Reports for Serious / Unlisted cases
☐ Domestic Consumer Report
☐ Adverse Event Summary
☐ Print Unsubmitted MedWatch Forms
☒ Include these summary tabulations / listings based on the set of cases presented in the line listing
* ER - Summary table
☐ Include these summary tabulations based on all cases
–None–
☐ Include these summary tabulations / listings based on the date range
–None–
* Exclude Follow-up Cases
☐ Additional Separate Page Numbering for UD Summaries

Advanced Condition used in this report:

Advanced Condition: nch_psur_nonserious_listed_hcp (Created by [redacted] C
Selection Criteria:
Advanced Condition nch_psur_nonserious_listed_hcp is overwritten by the following SQL statement:
SELECT DISTINCT cm.case_id FROM case_master cm, case_product cp, case_assess ca WHERE cm.case_id = cp.case_id AND cm.case_id = ca.case_id (+) AND (UPPER(cp.co_drug_code) like 'H-ZF+%' OR UPPER(cp.co_drug_code) like 'H-T05480+%') AND (cm.create_time between TO_DATE('01-Apr-2006', 'DD-MON-YYYY') and TO_DATE('31-Jan-2009', 'DD-MON-YYYY')) AND cp.drug_type = 1 AND cm.state_id > 1 AND (cm.rpt_type_id IN (1,3)) and ca.seriousness = 0 AND cm.case_id NOT IN (SELECT case_id FROM case_classifications WHERE classification_id IN ([redacted] B

Period: 01-Apr-2006 Through 31-Jan-2009

Ingredient: **SODIUM FLUORIDE**

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
Medically Confirmed (18)								
Event System Organ Class: Gastrointestinal disorders (1)								
[redacted]	Spontaneous Report	2 Years Female	**ZYMAFLUOR (NCH) / *Solution*** UNK [UNK]	Oral		30-MAR-2008 30-MAR-2008	Vomiting [VOMITING] *A 2-year-old child ingested accidentally half a vial of* Zymafluor [ACCIDENTAL DRUG INTAKE BY CHILD]	Complete Recovery
			UNK [UNK]	Oral	30-MAR-2008 to Unknown	30-MAR-2008	Ingested accidentally half a vial of Zymafluor [ACCIDENTAL OVERDOSE]	
	Case Narrative:	This pharmacist report combines initial information received on 30 Mar 2008, follow-up information received on 01 Apr 2008 and on 07 Apr 2008. This 2-year-old child usually treated with Zymafluor 0.114% solution (sodium fluoride) for caries prophylaxis ingested accidentally half a vial of Zymafluor. The child experienced vomiting within 30 seconds post ingestion which was very short and lasted for 1 minute. The child was given milky products: The final outcome was complete recovery. The reporting pharmacist considered that the event was not related to the drug. Follow-up report received from pharmacist on 30 Apr 2008. The reporting pharmacist confirmed the previous information and specified that the onset date was 30 Mar 2008. No other information available.					
Event System Organ Class: General disorders and administration site conditions (11)								
[redacted]	Spontaneous Report	23 Months Female	**ZYMAFLUOR (NCH) / Unknown** .25 mg [.25 mg-QD]	Oral			The child was asymptomatic and remained asymptomatic [NO ADVERSE EVENT]	Not Applicable
			UNK [ONCE/SINGLE]	Oral	09-OCT-2006 to 09-OCT-2006		Asymptomatic acute ingestion of unspecified number of Zymafluor tablets [ACCIDENTAL OVERDOSE] Asymptomatic acute ingestion [ACCIDENTAL DRUG INTAKE BY CHILD]	
	Case Narrative:	Physician report received via Health Authorities on 13 Oct 2006. A 23 months old child was on treatment with 1 tablet of Zymafluor (sodium fluoride) daily. The child ingested by himself/herself an unknown number of tablets. The child was hospitalized for 1 day with gastric lavage (based on the number of tablets in a box (200)). The gastric lavage has been done half an hour after the intake. The child was asymptomatic and remained asymptomatic. The physician considered the box too easy to open and not enough childproof. No further information provided. Upon medical internal review on 13 Nov 2006, of the follow-up received on 06 Nov 2006 by the paediatrician, the case was downgraded to non-serious. The reporting physician specified that the exact number of tablets ingested by the child, on 09 Oct 2006, was unknown. He considered the event as non-serious. The demographics of the child were completed. The physician stated that the closing system was quite easy to open (the information was given to Quality Assurance). It was also specified that the child returned at home after the stomach lavage and blood sampling for relevant lab tests. The physician confirmed that the child remained asymptomatic. Zymafluor was not restarted.					
[redacted]	Spontaneous Report	3 Years Female	**ZYMAFLUOR (NCH) / Unknown** *UNK [UNK]*	Oral		20-MAR-2007	No adverse reactions [NO ADVERSE EVENT] Accidental ingestion of 13 tablets [ACCIDENTAL *DRUG INTAKE BY CHILD]*	Not Applicable
			UNK [13 DF-UNK]	Oral	20-MAR-2007 to 20-MAR-2007		Accidental ingestion of 13 tablets. [ACCIDENTAL OVERDOSE]	
	Case Narrative:	This report combined initial pharmacist information received on 20 Mar 2007 and follow-up pharmacist information received on 02 Apr 2007. A 3-year old child developed no adverse reaction after accidental ingestion of 13 tablets of Zymafluor 0.25 mg (sodium fluoride) on 20 Mar 2007. Zymafluor was discontinued.						
[redacted]	Spontaneous Report	3 Years Male	**ZYMAFLUOR (NCH) / Tablet** 1 DF [1 DF-QD]	Oral	Unknown to 03-MAY-2007	04-MAY-2007	Asymptomatic acute ingestion [NO ADVERSE EVENT] Amount ingested was about 20 tablets [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
			20 DF [20 DF-ONCE/SINGLE]	Oral	04-MAY-2007 to 04-MAY-2007		Amount ingested was about 20 tablets [ACCIDENTAL OVERDOSE]	

[2] Non-Medically Confirmed.

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
		Case Narrative:	Initial pharmacist report received on 04 May 2007: A 3 year-old young boy ingested the remaining content of a vial of Zymafluor 0,5 mg tablets (sodium fluoride). The amount ingested was about 20 tablets, ie 10 mg or 0,67 mg/kg. The pharmacist called the anti-poison centre who confirmed that there was no special risk and that no special measure was necessary, except giving milk to drink to the child. They suggested to discontinue the treatment for one month. The product was discontinued. At time of report, this event remained an asymptomatic acute ingestion. Follow-up information received on 08 Jun 2007 from a pharmacist: Patient's initials as well as his weight were changed. The acute ingestion was confirmed and the child was asymptomatic. Treatment with Zymafluor was discontinued. It was unknown whether the product was resumed.					
[redacted]	Spontaneous Report	2 Years Female	**ZYMAFLUOR (NCH) / Tablet** 50 mg [50 mg-QD] UNK [UNK]	Oral Oral			The girl remained asymptomatic [NO ADVERSE EVENT] A 2-years-old girl ingested more or less 40 tabs of Zymafluor [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
		Case Narrative:	Initial report received on 26 Sep 2007 from physician and patient's mother: This 2-year-old child ingested more or less 40 tabs of Zymafluor 0.50 mg (sodium fluoride) approximately 4 hours prior to the report. The number of ingested tablets was limited since many tablets had been spitted out. The child remained asymptomatic.					
[redacted]	Spontaneous Report	1 Years Female	**ZYMAFLUOR (NCH) / Unknown** UNK [UNK] .25 mg [.25 mg-QD]	Oral Oral	25-JAN-2008 to 25-MAR-2008 MAR-2008 Ongoing	25-JAN-2008 25-JAN-2008	No side reactions [NO ADVERSE EVENT] Accidentally treated with a daily dose of 4x1 tablets of Zymafluor 0.25mg [INCORRECT DOSE ADMINISTERED] The pharmacist had recommened to administer a daily dose of 4 tablets / overdosage [OVERDOSE]	Not Applicable
		Product Name:	BUDIAIR (BUDESONIDE) Concom,					
		Case Narrative:	This physician report combines initial information received on 26 Mar 2008 and follow-up information received on 27 Mar 2008. This 1-year-old child was accidentally treated with a daily dose of 4x1 tablets of Zymafluor 0.25 mg (sodium fluoride) on recommendation of a local pharmacist from 29 Jan 2008 to 25 Mar 2008. No side reactions were observed. Zymafluor 0.25 mg was temporarily discontinued for 3 weeks. Follow-up report received from physician on 21 Apr 2008. The physician reported an overdosage with a daily dose of 4 tablets of Zymafluor 0.25 mg from 25 Jan 2008 to 25 Mar 2008. According to the mother, the pharmacist had recommended to administer a daily dose of 4 tablets. No side reactions were reported. The daily dose of Zymafluor 0.25 mg was reduced to 1 tablet and the treatment was ongoing at the time of report.					
[redacted]	Spontaneous Report	3 Years Female	**ZYMAFLUOR (NCH) / Tablet** 10 mg [UNK]	Oral	19-SEP-2008 to 19-SEP-2008	19-SEP-2008 19-SEP-2008	No side reactions [NO ADVERSE EVENT] A three year old child took a maximum of twenty tablets [ACCIDENTAL DRUG INTAKE BY CHILD] A 3-year-old female child accidentally ingested a maximum of 20 tablets of Zymafluor [ACCIDENTAL OVERDOSE]	Not Applicable
		Patient Relevant History:	Historical Drug; ([redacted] ZYMAFLUOR Note: Was treated with Zymafluor 0.25mg since birth					
		Case Narrative:	This pharmacist report combines initial information received on 19 Sep 2008 and a follow-up received 23 Sep 2008. A 3-year-old female child accidentally ingested a maximum of 20 tablets of Zymafluor 0.5 mg (sodium fluoride) on 19 Sep 2008. The product was discontinued on the same day and the child took plenty of milk on recommendation from the consulted poison hotline. No side reactions were reported. Final outcome was complete recovery. Follow-report received from the pharmacist on 15 Oct 2008. The reporting pharmacist specified that the patient was treated with Zymafluor 0.25 mg since birth and then later with Zymafluor 0.5 mg. No side reactions were reported. But the reporter filled in a reaction duration of 1 hour (conflicting data). The product was stopped. The final outcome was complete recovery.					

[2] Non-Medically Confirmed.

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
[redacted]	Spontaneous Report	2 Years Female	**ZYMAFLUOR (NCH) / Tablet** UNK [UNK]	Oral	25-NOV-2008 to 25-NOV-2008	25-NOV-2008 25-NOV-2008 25-NOV-2008	No side reactions [NO ADVERSE EVENT] Two-year-old child accidentally took five tablets of Zymafluor [ACCIDENTAL DRUG INTAKE BY CHILD] Two-year-old child accidentally took five tablets of Zymafluor. [ACCIDENTAL OVERDOSE]	Not Applicable
	Case Narrative:	Initial pharmacist report received on 25 Nov 2008. This 2-year-old female child accidentally took five tablets of Zymafluor (sodium fluoride) 0.25 mg on 25 Nov 2008. Zymafluor 25 mg was discontinued on the same day. At the time of this report, no side reactions had been reported. Final outcome was unknown. Follow-up information was ongoing.						
[redacted]	Spontaneous Report	2 Years	**ZYMAFLUOR (NCH) / Tablet** 5 mg [5 mg-ONCE/SINGLE]	Oral	11-DEC-2008 to 11-DEC-2008	Onset after therapy initiation: 1 day 11-DEC-2008 11-DEC-2008	No side reactions reported [NO ADVERSE EVENT] The child ate unattended 20 tablets [ACCIDENTAL DRUG INTAKE BY CHILD] The child ate unattended 20 tablets. [ACCIDENTAL OVERDOSE]	Not Applicable
	Case Narrative:	This pharmacist report combines initial information received 11 Dec 2008 and a follow-up report received 22 Dec 2008. This 2 year old child ate unattended 20 tablets of Zymafluor (sodium fluoride) 0.25mg as a single dose (5mg) on 11 Dec 2008. The product was discontinued on 11 Dec 2008. No adverse events were reported. Final outcome was unknown.						
[redacted]	Spontaneous Report	3 Years Male	**ZYMAFLUOR (NCH) / Tablet** UNK [UNK]	Oral	23-MAY-2008 to Unknown	23-MAY-2008	No symptoms occured [NO ADVERSE EVENT] 3 year-old child ingested 10 tablets of Zymafluor 0.50 mg [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
	Case Narrative:	Initial pharmacist report received on 06 Jun 2008: This 3 year-old child ingested 10 tablets of Zymafluor 0.50 mg (sodium fluoride) on 23 May 2008. No symptoms occured. Final outcome was not reported. Follow-up report received on 09 Jul 2008 from the child's parents. They confirmed that no manifestation occurred and no physician was consulted. Upon internal review, the event Accidental overdose was deleted.						
[redacted]	Spontaneous Report	6 Years Male	**ZYMAFLUOR (NCH) / Tablet** UNK [UNK]	Oral	23-MAY-2008 to Unknown		No symptoms occured [NO ADVERSE EVENT] 6 year-old child ingested 10 tablets of Zymafluor 0.05 mg [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
	Case Narrative:	Initial pharmacist report received on 06 Jun 2008: This 6 year-old child ingested 10 tablets of Zymafluor 0.50 mg (sodium fluoride) on 23 May 208. No symptoms occurred. Follow-up report received on 09 Jul 2008 from the child's parents. They confirmed that no manifestation occurred and no physician was consulted.						
[redacted]	Spontaneous Report	33 Months Male	**ZYMAFLUOR (NCH) / Unknown** 25 mg [25 mg-ONCE/SINGLE]	Oral	16-OCT-2008 to 16-OCT-2008	OCT-2008 16-OCT-2008 16-OCT-2008	No symptom occurred [NO ADVERSE EVENT] Ingested half of the content of a Zymafluor 0.5mg box [ACCIDENTAL DRUG INTAKE BY CHILD] Ingested half of the content of a Zymafluor 0.5mg box. [ACCIDENTAL OVERDOSE]	Not Applicable
	Case Narrative:	This pharmacist report combines initial information received on 16 Oct 2008 and follow-up information received on 20 Oct 2008. A 33-month-old baby ingested half of the content of a Zymafluor 0.5mg (sodium fluoride) box on 16 Oct 2008. The total dose ingested was of 25mg (i.e. 1.7mg/kg). No symptom occurred.						
Event System Organ Class: Injury, poisoning and procedural complications (6)								
[redacted]	Spontaneous Report	6 Years Female	**ZYMAFLUOR (NCH) / Tablet** 40 DF [40 DF-ONCE/SINGLE]	Oral			6 year-old ingested about 40 tablets of Zymafluor [ACCIDENTAL OVERDOSE] 6 year-old ingested about 40 tablets of Zymafluor. [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
	Case Narrative:	Pharmacist report received on 11 Feb 2007: A 6 year-old girl, who was 26 kg, ingested about 40 tablets of Zymafluor 0,5 mg (sodium fluoride) (i.e. 0,76 mg/kg). The pharmacist advised the mother to give milky products to the child. No further information was provided. (the friend of the child also ingested Zymafluor - see related case [redacted]						

[2] Non-Medically Confirmed.

Period: 01-Apr-2006 Through 31-Jan-2009

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
[redacted]	Spontaneous Report	6 Years Female	**ZYMAFLUOR (NCH) / Tablet** 40 DF [40 DF-ONCE/SINGLE]	Oral			6-year-old little girl who ingested 40 tablets [ACCIDENTAL OVERDOSE] 6-year-old little girl who ingested 40 tablets. [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
	Case Narrative:	Pharmacist report received on 11 Feb 2007: A 6 year-old girl, who was 28 kg, ingested 40 tablets of Zymafluor 0,5 mg (sodium fluoride), (i.e. 0,71 mg/kg). The pharmacist advised the mother to give milky products to her daughter. The little girl shared the product with a friend of her (see related case [redacted] No further information was provided.						
[redacted]	Spontaneous Report	21 Years Female	**ZYMAFLUOR (NCH) / Unknown** 1 mg [1 mg-QD]	Oral	14-OCT-2008 Ongoing	14-OCT-2008	Pregnant woman (5th month) was prescribed Zymafluor [DRUG EXPOSURE DURING PREGNANCY]	Not Applicable
	Product Name:	TARDYFERON (FERROUS SULFATE) Concom, UVEDOSE (COLECALCIFEROL) Concom, dose: [redacted]						
	Case Narrative:	Initial pharmacist report received on 15 Oct 2008. This 21-year-old pregnant woman (5th month) was prescribed Zymafluor (sodium fluoride) for caries prophylaxis. The therapy was started on 14 Oct 2008. Zymafluor treatment was ongoing at the time of report. Non significant follow-up pharmacist report received on 06 Jan 2009: The pharmacist reported that follow-up was not possible.						
[redacted]	Spontaneous Report	27 Years Female	**ZYMAFLUOR (NCH) / Unknown** 1 mg [1 mg-QD]	Oral	09-DEC-2008 to Unknown	09-DEC-2008	Use of Zymafluor in a pregnant woman [DRUG EXPOSURE DURING PREGNANCY]	Not Applicable
	Product Name:	SALBUTAMOL (SALBUTAMOL) Concom,						
	Case Narrative:	Initial pharmacist report received on 09 Dec 2008. This 27-year-old female patient was in her 7th month of pregnancy and she was prescribed Zymafluor (sodium fluoride) 1mg per day on the 09 Dec 2008, for "protection of her very spoiled teeth". Follow-up information has been requested.						
[redacted]	Spontaneous Report	Female	**ZYMAFLUOR (NCH) / Tablet** UNK [.5 mg-UNK]	Oral	50 day(s)		Administered Zymafluor 0.50 mg tablets instead of 0.25 mg [INCORRECT DOSE ADMINISTERED]	Not Applicable
	Case Narrative:	Initial pharmacist report received on 04 Feb 2008. This 18-19-month-old child and her twin sister (see case [redacted] were administered Zymafluor 0.50 mg tablets (sodium fluoride) for 50 days, on a pharmacist advice, instead of 0.25 mg.						
[redacted]	Spontaneous Report	Female	**ZYMAFLUOR (NCH) / Tablet** UNK [.5 mg-UNK]	Oral			A 18-19-month-old child and her twin sister were administered Zymafluor 0.50 mg tablets [INCORRECT DOSE ADMINISTERED]	Not Applicable
	Case Narrative:	Initial pharmacist report received on 04 Feb 2008. A 18-19-month-old child and her twin sister (see related case [redacted] were administered Zymafluor 0.50 mg tablets (sodium fluoride) for 50 days, under pharmacist advice, instead of 0.25 mg. No further information was provided.						

Total number of case entries printed in the Medically Confirmed section: 18
Total number of cases printed in the Medically Confirmed section: 18
Total number of case entries printed: 18
Total number of cases printed: 18

B

[2] Non-Medically Confirmed.

Summary Tabulation

For All Products (Number of Events)
For the cases in this report

System Organ Class (SOC)	Preferred Term	Report Type: Spontaneous Report	Total
Gastrointestinal disorders	Vomiting	1	**1**
	SubTotal	**1**	**1**
General disorders and administration site conditions	No adverse event	11	**11**
	SubTotal	**11**	**11**
Injury, poisoning and procedural complications	Accidental drug intake by child	13	**13**
	Accidental overdose	10	**10**
	Drug exposure during pregnancy	2	**2**
	Incorrect dose administered	3	**3**
	Overdose	1	**1**
	SubTotal	**29**	**29**
Total		**41**	**41**

[2] Non-Medically Confirmed.

Period: 01-Apr-2006 Through 31-Jan-2009

Category: NCH PSURs + Add.

Sub Category:

Report Name: App 3.2.1 - Zymafluor [redacted] A

Agency Name: (No Specific Agency)

Header

Report# Line listing

Report Title App 3.2.1 - Zymafluor - Serious spontaneous non-HCP reports

☒ Ingredient SODIUM FLUORIDE

☐ Trade Name ZYMAFLUOR (NCH) (Unknown,), SODIUM FLUORIDE (NCH) (Solution,), ZYMAFLUOR (NCH) (Drops,), ZYMAFLUOR NA FLUORIDE (NCH) (Drops,), ZYMAFLUOR (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Unknown,), FLUREXAL (NCH) (Solution,), ZYMAFLUOR NA FLUORIDE (NCH) (Tablet,), ZYMAFLUOR NA FLUORIDE (NCH) (Unknown,), ZYMAFLUOR...

☐ IBD

Report Footer

☒ Print all configuration criteria on separate cover pages (PDF Only)

☐ Allow access to report cases through Hit List

Products

Ingredient: SODIUM FLUORIDE

Indication: (All Indications)

Formulation: (All Formulations)

ZYMAFLUOR H-ZF+TAB(Tablet,)
ZYMAFLUOR H-T05480+TAB(Tablet,)
ZYMAFLUOR H-ZF+SOL(Solution,)
ZYMAFLUOR H-ZF+(Unknown,)
ZYMAFLUOR H-ZF+DRP(Drops,)
FLUREXAL H-T05480+EFCTAB(Enteric-film-coated Tablet,)
ZYMAFLUOR H-T05480+(Unknown,)

Inclusion Criteria

Spontaneous Report	☒ Listed ☒ Unlisted	☒ Related ☒ Non-Related		
☒ Serious ☐ Non-Serious	Datasheet	☐ HCP ☒ Non-HCP		
☒ Fatal ☒ Non-Fatal	<ALL>	☐ Primary Reporter Only		
Literature Case	☒ Listed ☒ Unlisted	☒ Related ☒ Non-Related		
☒ Serious ☐ Non-Serious	Datasheet	☐ HCP ☒ Non-HCP		
☒ Fatal ☒ Non-Fatal	<ALL>	☐ Primary Reporter Only		

Listedness Assessment

◉ Use assessment in cases

○ Re-assess cases against datasheet in effect at beginning

○ Re-assess cases against datasheet in effect at end

Advanced Condition (None)

☐ Use Datasheet Assessment for UDF Tabulations

☐ Age Groups

☐ Adult (18-69 Y) ☐ Neonate (0-1 Y) ☐ Elderly (70-199 Y) ☐ Adolescent (13-17 Y)

☐ Infant (1-2 Y) ☐ Unborn (<0 Y) ☐ Child (3-12 Y) ☐ Unknown

Date Range

Case Creation Date		Case Receipt Date
From	01-APR-2006	From
To	31-JAN-2009	To

☐ Expeditable Only ☒ Exclude Follow-up Cases
☒ Include Unlocked Cases

☒ Include Line Listing Data Elements

☐ As Determined Causality	☐ As Determined Listedness	☐ As Reported Causality	☒ Case Abbreviated Narrative
☐ Case Central Safety Date	☐ Case Classification	☐ Case Comment Text	☐ Case Initial Receipt Date
☒ Case Listedness	☒ Case Narrative	☒ Case Number	☒ Case Outcome
☒ Case Report Type	☐ Case Seriousness?	☐ Clinical EUDRACT Number	☐ Clinical Study Reference
☐ Company Agent Causality?	☒ Country of Incidence	☐ Death Cause	☐ Death Cause HLGT
☐ Death Cause HLT	☐ Death Cause LLT	☐ Death Cause SOC	☐ Death Cause as Reported
☐ Dosage Regimen Batch / Lot #	☒ Dosage Regimen Daily Dose	☒ Dosage Regimen Duration	☒ Dosage Regimen Frequency
☒ Dosage Regimen Route of Administration	☒ Dosage Regimen Start Date/Time	☐ Drug Dechallenge?	☐ Drug Rechallenge?
☒ Event Description as Reported	☒ Event Onset Date/Time	☒ Event Preferred Term	☐ Lab Data - Tabular
☐ Literature Author	☒ Literature Journal	☐ Literature Pgs	☐ Literature Title
☐ Literature Vol	☐ Literature Year	☐ Outcome of Event	☒ Patient Age
☒ Patient Gender	☐ Patient Initials	☐ Patient Randomization Number	☒ Patient Relevant History
☐ Patient Sponsor Identifier	☐ Patient Subject #	☐ Product Indication Coding Status	☐ Product Indication HLGT
☐ Product Indication HLT	☐ Product Indication LLT	☐ Product Indication PT	☐ Product Indication SOC
☐ Product Indication as reported	☐ Product Indication to be coded	☒ Product Name	☐ Product Name Report Inclusion
☐ Report Comment	☐ Report Submission Date	☐ Reporter Type	☐ Study Center ID
☐ Study Drug	☐ Study ID	☐ Study Other ID	☐ Study Protocol ID

Options

Group By	Non Medically Confirmed	☒ Ascending	☒ Page Break
	Event System Organ Class	☒ Ascending	☐ Page Break
	Case Listedness	☒ Ascending	☐ Page Break

Sort By Case Number

MedDRA Hierarchy from ◉ Cases ○ Dictionary for Events

☐ Print Only the Term ◉ Preferred ○ Lower Level
☐ Print Dose Text in place of regimen dose
☐ Indicate if case was expedited Previously
☒ English Language ☐ Local Language --None--
☐ Place non-medically confirmed cases at the end
☐ Include non-serious listed cases in Line Listing at the end
☐ Print Event Info (Serious, Un-Listed, Causal) as Column
◉ List cases only once, under the primary event
○ List cases under all events, details under the primary event

☐ Print Product Indication for the Product selected in the Report

☐ Include Index of Cases in Report
☐ Include Line Listing Tabulation
☐ Include Initial Cases ☐ Include Follow-up Cases
☐ Include Summary of Cases Missing Assessments
☐ Include Summary of Unlocked Cases
☐ Include Cumulative Summary
☐ Print CIOMS Reports for Serious / Unlisted cases
☐ Domestic Consumer Report
☐ Adverse Event Summary
☐ Print Unsubmitted MedWatch Forms
☒ Include these summary tabulations / listings based on the set of cases presented in the line listing
* ER - Summary table
☐ Include these summary tabulations based on all cases
--None--
☐ Include these summary tabulations / listings based on the date range
--None--
* Exclude Follow-up Cases
☐ Additional Separate Page Numbering for UD Summaries

Period: 01-Apr-2006 Through 31-Jan-2009

Ingredient: SODIUM FLUORIDE

Case Number	Country Source	Age Sex	Daily Dose [Dose Frequency]	Form / Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome

No Data Found

[2] Non-Medically Confirmed. [3] Unlocked Case.

Category: NCH PSURs + Add.

Sub Category:

Report Name: App 3.2.2 - Zymafluor[redacted] A

Agency Name: (No Specific Agency)

Header

Report# Line listing
Report Title App 3.2.2 - Zymafluor - Serious solicited suspected Non-HCP reports
☒ Ingredient SODIUM FLUORIDE
☐ Trade Name ZYMAFLUOR (NCH) (Unknown,), SODIUM FLUORIDE (NCH) (Solution,), ZYMAFLUOR (NCH) (Drops,), ZYMAFLUOR NA FLUORIDE (NCH) (Drops,), ZYMAFLUOR (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Unknown,), FLUREXAL (NCH) (Solution,), ZYMAFLUOR NA FLUORIDE (NCH) (Tablet,), ZYMAFLUOR NA FLUORIDE (NCH) (Unknown,), ZYMAFLUOR...
☐ IBD
Report Footer
☒ Print all configuration criteria on separate cover pages (PDF Only)
☐ Allow access to report cases through Hit List

Products

Ingredient: SODIUM FLUORIDE
Indication: (All Indications)
Formulation: (All Formulations)
ZYMAFLUOR H-T05480+TAB(Tablet,)
ZYMAFLUOR H-ZF+TAB(Tablet,)
ZYMAFLUOR H-ZF+SOL(Solution,)
ZYMAFLUOR H-ZF+(Unknown,)
ZYMAFLUOR H-ZF+DRP(Drops,)
FLUREXAL H-T05480+EFCTAB(Enteric-film-coated Tablet,)
ZYMAFLUOR H-T05480+(Unknown,)

Inclusion Criteria

Clinical Trial ☒ Listed ☒ Unlisted ☒ Related ☐ Non-Related
☒ Serious ☐ Non-Serious Datasheet ☐ HCP ☒ Non-HCP
☒ Fatal ☒ Non-Fatal <ALL> ☐ Primary Reporter Only

Listedness Assessment
- ◉ Use assessment in cases
- ○ Re-assess cases against datasheet in effect at beginning
- ○ Re-assess cases against datasheet in effect at end

Advanced Condition (None)

☐ Use Datasheet Assessment for UDF Tabulations

☐ **Age Groups**

☐ Adult (18-69 Y) ☐ Neonate (0-1 Y) ☐ Elderly (70-199 Y) ☐ Adolescent (13-17 Y)
☐ Infant (1-2 Y) ☐ Unborn (<0 Y) ☐ Child (3-12 Y) ☐ Unknown

Date Range

Case Creation Date		Case Receipt Date
From	01-APR-2006	From
To	31-JAN-2009	To

☐ Expeditable Only ☒ Exclude Follow-up Cases
☒ Include Unlocked Cases

☒ Include Line Listing Data Elements

☐ As Determined Causality	☐ As Determined Listedness	☐ As Reported Causality	☒ Case Abbreviated Narrative
☐ Case Central Safety Date	☐ Case Classification	☐ Case Comment Text	☐ Case Initial Receipt Date
☒ Case Listedness	☒ Case Narrative	☒ Case Number	☒ Case Outcome
☒ Case Report Type	☐ Case Seriousness?	☐ Clinical EUDRACT Number	☐ Clinical Study Reference
☐ Company Agent Causality?	☒ Country of Incidence	☐ Death Cause	☐ Death Cause HLGT
☐ Death Cause HLT	☐ Death Cause LLT	☐ Death Cause SOC	☐ Death Cause as Reported
☐ Dosage Regimen Batch / Lot #	☒ Dosage Regimen Daily Dose	☒ Dosage Regimen Duration	☒ Dosage Regimen Frequency
☒ Dosage Regimen Route of Administration	☒ Dosage Regimen Start Date/Time	☐ Drug Dechallenge?	☐ Drug Rechallenge?
☒ Event Description as Reported	☒ Event Onset Date/Time	☒ Event Preferred Term	☐ Lab Data - Tabular
☐ Literature Author	☒ Literature Journal	☐ Literature Pgs	☐ Literature Title
☐ Literature Vol	☐ Literature Year	☐ Outcome of Event	☒ Patient Age
☒ Patient Gender	☐ Patient Initials	☐ Patient Randomization Number	☒ Patient Relevant History
☐ Patient Sponsor Identifier	☐ Patient Subject #	☐ Product Indication Coding Status	☐ Product Indication HLGT
☐ Product Indication HLT	☐ Product Indication LLT	☐ Product Indication PT	☐ Product Indication SOC
☐ Product Indication as reported	☐ Product Indication to be coded	☒ Product Name	☐ Product Name Report Inclusion
☐ Report Comment	☐ Report Submission Date	☐ Reporter Type	☐ Study Center ID
☐ Study Drug	☐ Study ID	☐ Study Other ID	☐ Study Protocol ID

Options

Group By			
	Non Medically Confirmed	☒ Ascending	☒ Page Break
	Event System Organ Class	☒ Ascending	☐ Page Break
	Case Listedness	☒ Ascending	☐ Page Break

Sort By Case Number
MedDRA Hierarchy from ◉ Cases ○ Dictionary for Events
☐ Print Only the Term ◉ Preferred ○ Lower Level
☐ Print Dose Text in place of regimen dose
☐ Indicate if case was expedited Previously
☒ English Language ☐ Local Language --None--

☐ Place non-medically confirmed cases at the end
☐ Include non-serious listed cases in Line Listing at the end
☐ Print Event Info (Serious, Un-Listed, Causal) as Column
◉ List cases only once, under the primary event
○ List cases under all events, details under the primary event

☐ Print Product Indication for the Product selected in the Report

☐ Include Index of Cases in Report
☐ Include Line Listing Tabulation
  ☐ Include Initial Cases ☐ Include Follow-up Cases
☐ Include Summary of Cases Missing Assessments
☐ Include Summary of Unlocked Cases
☐ Include Cumulative Summary
☐ Print CIOMS Reports for Serious / Unlisted cases
☐ Domestic Consumer Report
☐ Adverse Event Summary
☐ Print Unsubmitted MedWatch Forms
☒ Include these summary tabulations / listings based on the set of cases presented in the line listing
  * ER - Summary table
☐ Include these summary tabulations based on all cases
  –None–
☐ Include these summary tabulations / listings based on the date range
  –None–
* Exclude Follow-up Cases
☐ Additional Separate Page Numbering for UD Summaries

Period: 01-Apr-2006 Through 31-Jan-2009

Ingredient: **SODIUM FLUORIDE**

Case Number	Country Source	Age Sex	Daily Dose [Dose Frequency]	Form / Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome

No Data Found

[2] Non-Medically Confirmed. [3] Unlocked Case.

Category: NCH PSURs + Add.

Sub Category:

Report Name: App 3.2.3-Zymafluor [redacted] A

Agency Name: (No Specific Agency)

Header

Report# Line listing
Report Title App 3.2.3 - Zymafluor - Non-serious unlisted spontaneous non-HCP reports
☒ Ingredient SODIUM FLUORIDE
☐ Trade Name ZYMAFLUOR (NCH) (Unknown,), SODIUM FLUORIDE (NCH) (Solution,), ZYMAFLUOR (NCH) (Drops,), ZYMAFLUOR NA FLUORIDE (NCH) (Drops,), ZYMAFLUOR (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Unknown,), FLUREXAL (NCH) (Solution,), ZYMAFLUOR NA FLUORIDE (NCH) (Tablet,), ZYMAFLUOR NA FLUORIDE (NCH) (Unknown,), ZYMAFLUOR...
☐ IBD
Report Footer
☒ Print all configuration criteria on separate cover pages (PDF Only)
☐ Allow access to report cases through Hit List

Products

Ingredient: SODIUM FLUORIDE
Indication: (All Indications)
Formulation: (All Formulations)
ZYMAFLUOR H-T05480+TAB(Tablet,)
ZYMAFLUOR H-ZF+TAB(Tablet,)
ZYMAFLUOR H-ZF+SOL(Solution,)
ZYMAFLUOR H-ZF+(Unknown,)
ZYMAFLUOR H-ZF+DRP(Drops,)
FLUREXAL H-T05480+EFCTAB(Enteric-film-coated Tablet,)
ZYMAFLUOR H-T05480+(Unknown,)

Inclusion Criteria

Literature Case	☐ Listed	☒ Unlisted	☒ Related	☒ Non-Related	
☐ Serious ☒ Non-Serious	Datasheet		☐ HCP	☒ Non-HCP	
☐ Fatal ☒ Non-Fatal	<ALL>		☐ Primary Reporter Only		
Spontaneous Report	☐ Listed	☒ Unlisted	☒ Related	☒ Non-Related	
☐ Serious ☒ Non-Serious	Datasheet		☐ HCP	☒ Non-HCP	
☐ Fatal ☒ Non-Fatal	<ALL>		☐ Primary Reporter Only		

Listedness Assessment
◉ Use assessment in cases
○ Re-assess cases against datasheet in effect at beginning
○ Re-assess cases against datasheet in effect at end

Advanced Condition (None)

☐ Use Datasheet Assessment for UDF Tabulations

☐ Age Groups

☐ Adult (18-69 Y) ☐ Neonate (0-1 Y) ☐ Elderly (70-199 Y) ☐ Adolescent (13-17 Y)

☐ Infant (1-2 Y) ☐ Unborn (<0 Y) ☐ Child (3-12 Y) ☐ Unknown

Date Range

Case Creation Date		Case Receipt Date
From	01-APR-2006	From
To	31-JAN-2009	To

☐ Expediteable Only ☒ Exclude Follow-up Cases
☒ Include Unlocked Cases

☒ Include Line Listing Data Elements

☐ As Determined Causality	☐ As Determined Listedness	☐ As Reported Causality	☒ Case Abbreviated Narrative
☐ Case Central Safety Date	☐ Case Classification	☐ Case Comment Text	☐ Case Initial Receipt Date
☐ Case Listedness	☒ Case Narrative	☒ Case Number	☒ Case Outcome
☒ Case Report Type	☐ Case Seriousness?	☐ Clinical EUDRACT Number	☐ Clinical Study Reference
☐ Company Agent Causality?	☒ Country of Incidence	☐ Death Cause	☐ Death Cause HLGT
☐ Death Cause HLT	☐ Death Cause LLT	☐ Death Cause SOC	☐ Death Cause as Reported
☐ Dosage Regimen Batch / Lot #	☒ Dosage Regimen Daily Dose	☒ Dosage Regimen Duration	☒ Dosage Regimen Frequency
☒ Dosage Regimen Route of Administration	☒ Dosage Regimen Start Date/Time	☐ Drug Dechallenge?	☐ Drug Rechallenge?
☒ Event Description as Reported	☒ Event Onset Date/Time	☒ Event Preferred Term	☐ Lab Data - Tabular
☐ Literature Author	☒ Literature Journal	☐ Literature Pgs	☐ Literature Title
☐ Literature Vol	☐ Literature Year	☐ Outcome of Event	☒ Patient Age
☒ Patient Gender	☐ Patient Initials	☐ Patient Randomization Number	☒ Patient Relevant History
☐ Patient Sponsor Identifier	☐ Patient Subject #	☐ Product Indication Coding Status	☐ Product Indication HLGT
☐ Product Indication HLT	☐ Product Indication LLT	☐ Product Indication PT	☐ Product Indication SOC
☐ Product Indication as reported	☐ Product Indication to be coded	☒ Product Name	☐ Product Name Report Inclusion
☐ Report Comment	☐ Report Submission Date	☐ Reporter Type	☐ Study Center ID
☐ Study Drug	☐ Study ID	☐ Study Other ID	☐ Study Protocol ID

Options

Group By			
	Non Medically Confirmed	☒ Ascending	☒ Page Break
	Event System Organ Class	☒ Ascending	☐ Page Break

Sort By Case Number

MedDRA Hierarchy from ◉ Cases ○ Dictionary for Events

☐ Print Only the Term ◉ Preferred ○ Lower Level

☐ Print Dose Text in place of regimen dose
☐ Indicate if case was expedited Previously
☒ English Language ☐ Local Language --None--
☐ Place non-medically confirmed cases at the end
☐ Include non-serious listed cases in Line Listing at the end
☐ Print Event Info (Serious, Un-Listed, Causal) as Column
◉ List cases only once, under the primary event
○ List cases under all events, details under the primary event

☐ Print Product Indication for the Product selected in the Report

☐ Include Index of Cases in Report
☐ Include Line Listing Tabulation
☐ Include Initial Cases ☐ Include Follow-up Cases
☐ Include Summary of Cases Missing Assessments
☐ Include Summary of Unlocked Cases
☐ Include Cumulative Summary
☐ Print CIOMS Reports for Serious / Unlisted cases
☐ Domestic Consumer Report
☐ Adverse Event Summary
☐ Print Unsubmitted MedWatch Forms
☒ Include these summary tabulations / listings based on the set of cases presented in the line listing
* ER - Summary table
☐ Include these summary tabulations based on all cases
--None--
☐ Include these summary tabulations / listings based on the date range
--None--
* Exclude Follow-up Cases
☐ Additional Separate Page Numbering for UD Summaries

Period: 01-Apr-2006 Through 31-Jan-2009

Ingredient: **SODIUM FLUORIDE**

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
Non-Medically Confirmed (4)								
Event System Organ Class: General disorders and administration site conditions (1)								
[redacted]	Spontaneous Report		**ZYMAFLUOR (NCH) / Unknown** UNK [UNK]	Oral	24-DEC-2008 to Unknown	25-DEC-2008 25-DEC-2008	Rash and discomfort on the face and neck [DISCOMFORT] Rash and discomfort on the face and neck [RASH]	Condition Improving
Event System Organ Class: Psychiatric disorders (2)								
[redacted]	Spontaneous Report	3 Years	**ZYMAFLUOR (NCH) / Tablet** UNK [UNK]	Oral		10-FEB-2008 10-FEB-2008	The child misused Zymafluor 0.25 mg [INTENTIONAL DRUG MISUSE] Overdose of around 90 tabs [OVERDOSE]	Complete Recovery
	Case Narrative:		This consumer report combines initial information received on 10 Feb 2008 and a follow-up information received on 12 Feb 2008. This child took Zymafluor 0.25 mg (sodium fluoride) for prophylaxis of dental caries. On 10 Feb 2008, the child misused Zymafluor 0.25 mg. The child took an overdose of around 90 tabs of Zymafluor as a single dose. No further information was provided.					
[redacted]	Spontaneous Report	2 Years Female	**ZYMAFLUOR (NCH) / Tablet** 2.5 mg [2.5 mg-ONCE/SINGLE]	Oral			Child misused Zymafluor 0.25 mg [INTENTIONAL DRUG MISUSE] Overdose around 10 tablets [ACCIDENTAL OVERDOSE]	Not Applicable
	Case Narrative:		Initial report received on 02 Apr 2008 from the consumer's mother: This 2 year-old child misused Zymafluor 0.25 mg (sodium fluoride) on 02 Apr 2008. The child took an overdose of around 10 tabs of Zymafluor as a single dose. No further information was provided.					
Event System Organ Class: Skin and subcutaneous tissue disorders (1)								
[redacted]	Spontaneous Report	3 Years Male	**ZYMAFLUOR (NCH) / Unknown** UNK [.25 mg-UNK]	Oral	2006 to Unknown		Covered in sweat [HYPERHIDROSIS] Unclear attacks [ADVERSE DRUG REACTION]	Complete Recovery
	Case Narrative:		Initial consumer report received on 17 Oct 2007. This 3-year-old child was treated with Zymafluor 0.25 mg (sodium fluoride) for caries prophylaxis and developed intermittently unclear attacks and was sometimes covered in sweat after these attacks. After several hospitalizations, the specific diagnostics revealed a positive allergy test for peanut and hazelnut. The treatment with Zymafluor was stopped 3-4 weeks prior to the date of this report. The reactions did not recur and the outcome was recovery.					

Total number of case entries printed in the Non-Medically Confirmed section: 4
Total number of cases printed in the Non-Medically Confirmed section: 4
Total number of case entries printed: 4
Total number of cases printed: 4

B

[2] Non-Medically Confirmed.

Summary Tabulation

For All Products (Number of Events)
For the cases in this report

System Organ Class (SOC)	Preferred Term	Report Type: Spontaneous Report	Total
General disorders and administration site conditions	Adverse drug reaction	1	1
	Discomfort	1	1
	SubTotal	**2**	**2**
Injury, poisoning and procedural complications	Accidental overdose	1	1
	Overdose	1	1
	SubTotal	**2**	**2**
Psychiatric disorders	Intentional drug misuse	2	2
	SubTotal	**2**	**2**
Skin and subcutaneous tissue disorders	Hyperhidrosis	1	1
	Rash	1	1
	SubTotal	**2**	**2**
Total		**8**	**8**

[2] Non-Medically Confirmed.

Period: 01-Apr-2006 Through 31-Jan-2009

Category: NCH PSURs + Add.

Sub Category:

Report Name: App 3.2.4-Zymafluo[redacted] A

Agency Name: (No Specific Agency)

Header

Report# Line listing
Report Title App 3.2.4 - Zymafluor - Non-serious listed spontaneous non-HCP reports
☒ Ingredient SODIUM FLUORIDE
☐ Trade Name ZYMAFLUOR (NCH) (Unknown,), SODIUM FLUORIDE (NCH) (Solution,), ZYMAFLUOR (NCH) (Drops,), ZYMAFLUOR NA FLUORIDE (NCH) (Drops,), ZYMAFLUOR (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Enteric-film-coated Tablet,), SODIUM FLUORIDE (NCH) (Unknown,), FLUREXAL (NCH) (Solution,), ZYMAFLUOR NA FLUORIDE (NCH) (Tablet,), ZYMAFLUOR NA FLUORIDE (NCH) (Unknown,), ZYMAFLUOR...

☐ IBD
Report Footer
☒ Print all configuration criteria on separate cover pages (PDF Only)
☐ Allow access to report cases through Hit List

Products

Ingredient: SODIUM FLUORIDE
Indication: (All Indications)
Formulation: (All Formulations)
ZYMAFLUOR H-T05480+TAB(Tablet,)
ZYMAFLUOR H-ZF+TAB(Tablet,)
ZYMAFLUOR H-ZF+SOL(Solution,)
ZYMAFLUOR H-ZF+(Unknown,)
ZYMAFLUOR H-ZF+DRP(Drops,)
FLUREXAL H-T05480+EFCTAB(Enteric-film-coated Tablet,)
ZYMAFLUOR H-T05480+(Unknown,)

Inclusion Criteria

Spontaneous Report		☒ Listed	☐ Unlisted	☒ Related	☒ Non-Related
☐ Serious	☒ Non-Serious	Datasheet		☐ HCP	☒ Non-HCP
☐ Fatal	☒ Non-Fatal	<ALL>		☐ Primary Reporter Only	
Literature Case		☒ Listed	☐ Unlisted	☒ Related	☒ Non-Related
☐ Serious	☒ Non-Serious	Datasheet		☐ HCP	☒ Non-HCP
☐ Fatal	☒ Non-Fatal	<ALL>		☐ Primary Reporter Only	

Listedness Assessment
◉ Use assessment in cases
○ Re-assess cases against datasheet in effect at beginning
○ Re-assess cases against datasheet in effect at end

Advanced Condition (None)

☐ Use Datasheet Assessment for UDF Tabulations

☐ Age Groups

☐ Adult (18-69 Y) ☐ Neonate (0-1 Y) ☐ Elderly (70-199 Y) ☐ Adolescent (13-17 Y)
☐ Infant (1-2 Y) ☐ Unborn (<0 Y) ☐ Child (3-12 Y) ☐ Unknown

Date Range

Case Creation Date		Case Receipt Date
From	01-APR-2006	From
To	31-JAN-2009	To

☐ Expeditable Only ☒ Exclude Follow-up Cases
☒ Include Unlocked Cases

☒ Include Line Listing Data Elements

☐ As Determined Causality	☐ As Determined Listedness	☐ As Reported Causality	☒ Case Abbreviated Narrative
☐ Case Central Safety Date	☐ Case Classification	☐ Case Comment Text	☐ Case Initial Receipt Date
☐ Case Listedness	☒ Case Narrative	☒ Case Number	☒ Case Outcome
☒ Case Report Type	☐ Case Seriousness?	☐ Clinical EUDRACT Number	☐ Clinical Study Reference
☐ Company Agent Causality?	☒ Country of Incidence	☐ Death Cause	☐ Death Cause HLGT
☐ Death Cause HLT	☐ Death Cause LLT	☐ Death Cause SOC	☐ Death Cause as Reported
☐ Dosage Regimen Batch / Lot #	☒ Dosage Regimen Daily Dose	☒ Dosage Regimen Duration	☒ Dosage Regimen Frequency
☒ Dosage Regimen Route of Administration	☒ Dosage Regimen Start Date/Time	☐ Drug Dechallenge?	☐ Drug Rechallenge?
☒ Event Description as Reported	☒ Event Onset Date/Time	☒ Event Preferred Term	☐ Lab Data - Tabular
☐ Literature Author	☒ Literature Journal	☐ Literature Pgs	☐ Literature Title
☐ Literature Vol	☐ Literature Year	☐ Outcome of Event	☒ Patient Age
☒ Patient Gender	☐ Patient Initials	☐ Patient Randomization Number	☒ Patient Relevant History
☐ Patient Sponsor Identifier	☐ Patient Subject #	☐ Product Indication Coding Status	☐ Product Indication HLGT
☐ Product Indication HLT	☐ Product Indication LLT	☐ Product Indication PT	☐ Product Indication SOC
☐ Product Indication as reported	☐ Product Indication to be coded	☒ Product Name	☐ Product Name Report Inclusion
☐ Report Comment	☐ Report Submission Date	☐ Reporter Type	☐ Study Center ID
☐ Study Drug	☐ Study ID	☐ Study Other ID	☐ Study Protocol ID

Options

Group By			
	Non Medically Confirmed	☒ Ascending	☒ Page Break
	Event System Organ Class	☒ Ascending	☐ Page Break

Sort By Case Number
MedDRA Hierarchy from ◉ Cases ○ Dictionary for Events
☐ Print Only the Term ◉ Preferred ○ Lower Level

☐ Print Dose Text in place of regimen dose
☐ Indicate if case was expedited Previously
☒ English Language ☐ Local Language --None--
☐ Place non-medically confirmed cases at the end
☐ Include non-serious listed cases in Line Listing at the end
☐ Print Event Info (Serious, Un-Listed, Causal) as Column
◉ List cases only once, under the primary event
○ *List cases under all events, details under the primary event*

☐ Print Product Indication for the Product selected in the Report

☐ Include Index of Cases in Report
☐ Include Line Listing Tabulation
☐ Include Initial Cases ☐ Include Follow-up Cases
☐ Include Summary of Cases Missing Assessments
☐ Include Summary of Unlocked Cases
☐ Include Cumulative Summary
☐ Print CIOMS Reports for Serious / Unlisted cases
☐ Domestic Consumer Report
☐ Adverse Event Summary
☐ Print Unsubmitted MedWatch Forms
☒ Include these summary tabulations / listings based on the set of cases presented in the line listing
* ER - Summary table
☐ Include these summary tabulations based on all cases
--None--
☐ Include these summary tabulations / listings based on the date range
--None--
* Exclude Follow-up Cases
☐ Additional Separate Page Numbering for UD Summaries

Period: 01-Apr-2006 Through 31-Jan-2009

Ingredient: **SODIUM FLUORIDE**

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
Non-Medically Confirmed (15)								
Event System Organ Class: Gastrointestinal disorders (1)								
[redacted]	Spontaneous Report	2 Years Male	ZYMAFLUOR (NCH) / Tablet UNK [UNK]	Oral	02-MAR-2008 to 02-MAR-2008	02-MAR-2008 02-MAR-2008	Soft stools [DIARRHOEA] 2-years old boy ingested about 100 tablets of Zymafluor [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
	Case Narrative:		This report combines initial information received on 03 Mar 2008 and follow-up information received on 13 Mar 2008 by the consumerâ??s mother. This 2-years old boy ingested about 100 tablets of Zymafluor 0.25mg (sodium fluoride) (i.e 2.27 mg/kg) on 02 Mar 2008. The mother gave him milky products within one hour after Zymafluor ingestion. The consumer had soft stools in the evening 3 hours after the ingestion. Those symptoms completely disappeared and the stools were normal the next morning. No physician was not consulted. Final outcome: completely recovered.					
Event System Organ Class: General disorders and administration site conditions (11)								
[redacted]	Spontaneous Report	3 Years	ZYMAFLUOR (NCH) / Unknown UNK [.25 mg-UNK]	Oral	03-JUL-2006 to 03-JUL-2006	03-JUL-2006	Child developed no adverse reaction [NO ADVERSE EVENT]	Not Applicable
						03-JUL-2006	Accidental intake [ACCIDENTAL DRUG INTAKE BY CHILD]	
						03-JUL-2006	Intake of approximately 150-170 tablets of Zymafluor [ACCIDENTAL OVERDOSE]	
	Case Narrative:		This initial report was received from consumer's mother on 6 Jul 2006. The child took accidentally approximately 150 - 170 tablets of Zymafluor (sodium fluoride) and did not experienced adverse reaction. Treatment was stopped. The outcome was unknown.					
[redacted]	Spontaneous Report	Male	ZYMAFLUOR (NCH) / Tablet .5 mg [.5 mg-QD] UNK [.5 mg-UNK]	Oral	2003 to Unknown		No event occured after ingestion [NO ADVERSE EVENT] Asymptomatic acute ingestion [ACCIDENTAL DRUG INTAKE BY CHILD] Maximum ingested dose is about 30 tablets [ACCIDENTAL OVERDOSE]	Not Applicable
	Product Name:		NUTRAMIGEN (PROTEIN HYDROLYSATE) Concom,					
	Patient Relevant History:		Hypersens. /Allergy; ([redacted]Hypersensitivity Note: Allergy to milk and milky products					
	Case Narrative:		This report combines initial information received on 18 Jun 2006 and follow-up information received on 29 Jun 2006 from consumer: The mother of a 2,5 years old boy found her son playing with a bottle of Zymafluor 0,5 mg (sodium fluoride). The mother could recover 54 tablets and according to the date of opening of this bottle (several weeks ago), the maximum ingested dose is about 30 tablets, ie 1.11 mg/kg. The mother produced a "mechanical" vomiting within minutes following ingestion. Because the child is allergic to milk and milky products, it was only possible to recommend the administration of his regular milk substitute (nutramigen) that contains 90 mg of calcium /100 ml. No event occurred after ingestion. The baby was treated with Motilium (domperidone).					
[redacted]	Spontaneous Report		ZYMAFLUOR (NCH) / Unknown UNK [.25 mg-UNK]	Oral	27-AUG-2007 to 27-AUG-2007		No reaction [NO ADVERSE EVENT] Accidentally took an unspecified amount of Zymafluor [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
	Case Narrative:		Initial report received on 27 Aug 2007 from the mother's consumer: a child accidentally took an unspecified amount of Zymafluor 0.25 mg tablets on 27 Aug 2007 and developed no reaction. The mother stated that she took an unspecified amount of tablets out of the mouth of her child. Zymafluor was discontinued.					
[2] [redacted]	Spontaneous Report	3 Years Male	ZYMAFLUOR (NCH) / Tablet UNK [UNK]	Oral	28-AUG-2007 to 28-AUG-2007	28-AUG-2007	No reaction [NO ADVERSE EVENT] 3-year-old child accidentally ingested 10 tablets of Zymafluor [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
	Case Narrative:		This consumer report combines initial information received on 28 Aug 2007 and follow-up information received on 04 Sep 2007. a 3-year-old child and another child (see case [redacted]ccidentally ingested 10 tablets of Zymafluor 0.25 mg (sodium fluoride) on 28 Aug 2007. No reaction was observed. The child was given plenty of milk. Zymafluor was discontinued.					

[2] Non-Medically Confirmed.

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
[redacted]	Spontaneous Report	1 Years Female	**ZYMAFLUOR (NCH) / Tablet** UNK [UNK]	Oral	28-AUG-2007 to 28-AUG-2007	28-AUG-2007	No reaction [NO ADVERSE EVENT] 1.5 year old child accidentally ingested 5 tablets of Zymalfuor [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
	Case Narrative:	This consumer report combines initial information received on 28 Aug 2007 and follow-up information received on 04 Sep 2007.: This 1.5 year old child and another child (see case CHNY2007DE03050) accidentally ingested 5 tablets of Zymafluor 0.25 mg (sodium fluoride) on 28 Aug 2007. No reaction was observed. The child was given plenty of milk. Zymafluor was discontinued.						
[redacted]	Spontaneous Report	2 Years Female	**ZYMAFLUOR (NCH) / Unknown** UNK [.25 mg-UNK]	Oral			Child remained asymptomatic [NO ADVERSE EVENT] 2.5 year old child inadvertently ingested an unknown amount of Zymafluor [ACCIDENTAL DRUG INTAKE BY CHILD]	Not Applicable
	Case Narrative:	Initial consumer report received on 18 Jul 2007: A 2.5 year-old child ingested an unknown amount of Zymafluor 0.25 mg (sodium fluoride) about half an hour prior to the report. No further information was provided. Follow-up information received on 03 Sep 2007 from consumer: the child remained asymptomatic. The child was given milk. No additional information was provided.						
[redacted]	Spontaneous Report		**ZYMAFLUOR (NCH) / Tablet** UNK [UNK]	Oral	FEB-2008 to FEB-2008	FEB-2008	No side reactions [NO ADVERSE EVENT] Child had taken too many tablets of Zymafluor [OVERDOSE]	Not Applicable
	Case Narrative:	Initial consumer report received on 14 Feb 2008. This unspecified child had taken too many tablets of Zymafluor (sodium fluoride) in Feb 2008. No side reactions were reported. Zymafluor was discontinued in Feb 2008. Final outcome was unknown.						
[redacted]	Spontaneous Report	2 Years Male	**ZYMAFLUOR (NCH) / Tablet** UNK [UNK]	Oral	16-JAN-2008 to FEB-2008		No side reaction was reported [NO ADVERSE EVENT] A 2-year-old child accidentally ingested a maximum of 3 tablets [ACCIDENTAL DRUG INTAKE BY CHILD] A 2-year-old child accidentally ingested a maximum of 3 tablets. [ACCIDENTAL OVERDOSE]	Not Applicable
	Case Narrative:	This consumer report combines initial information received on 03 Mar 2008 and a follow-up information received on 14 Mar 2008. This 2-year-old child accidentally ingested a maximum of 3 tablets of Zymafluor (sodium fluoride) as a single dose approximately on 29 Feb 2008. No side reaction was reported at the date of this report. Zymafluor therapy was still ongoing at the time of report.						
[redacted]	Spontaneous Report	2 Years Male	**ZYMAFLUOR (NCH) / Tablet** .5 mg [.5 mg-QD]	Oral	AUG-2007 to MAR-2008		No side reaction [NO ADVERSE EVENT] Accidentally treated with Zymafluor 0.5 mg instead of Zymafluor 0.25 mg [INCORRECT DOSE ADMINISTERED]	Not Applicable
	Product Name:	ELMEX (DECTAFLUR, SODIUM FLUORIDE) Concom,						
	Case Narrative:	Initial consumer report received on 25 Mar 2008. This 2.7 year-old child had been accidentally treated with daily dose of 1 tablet of Zymafluor 0.5 mg (sodium fluoride) instead of Zymafluor 0.25 mg (sodium fluoride) since Aug 2007. Zymafluor 0.5 mg was initially prescribed by the treating children's specialist. On recommendation, Zymafluor 0.5 mg was changed to Zymafluor 0.25 mg in Mar 2008. No side reactions were reported.						
[redacted]	Spontaneous Report	Female	**ZYMAFLUOR (NCH) / Tablet** UNK [UNK]	Oral			No side effect [NO ADVERSE EVENT] Used 10 mg daily [OVERDOSE]	Not Applicable
	Case Narrative:	Initial consumer report received on 18 Jan 2008. The consumer started Zymafluor (sodium fluoride) 1mg for otospongiosis (off label use) 8 months prior to this report. The consumer used 10 mg daily. No side effect was reported.						

B

[2] Non-Medically Confirmed.

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
[redacted]	Spontaneous Report	Male	**ZYMAFLUOR (NCH) / Tablet** 30 DF [30 DF-ONCE/SINGLE]	Oral		29-APR-2008	No side effect happened [NO ADVERSE EVENT] Child took around 30 tablets of Zymafluor 0.25 mg [ACCIDENTAL DRUG INTAKE BY CHILD] Child took around 30 tablets of Zymafluor 0.25 mg. [ACCIDENTAL OVERDOSE]	Not Applicable
	Case Narrative:		Initial consumer report received on 29 Apr 2008. This child took around 30 tablets of Zymafluor 0.25 mg (sodium fluoride) as a single dose on 29 Apr 2008. No side effect happened.					
Event System Organ Class: Injury, poisoning and procedural complications (2)								
[redacted]	Spontaneous Report	Female	**ZYMAFLUOR (NCH) / Tablet** UNK [UNK]	Oral	30-JUN-2006 to 30-JUN-2006	30-JUN-2006	Ingested accidentally 5-6 tablets of Zymafluor 0.25 mg [ACCIDENTAL DRUG INTAKE BY CHILD] *- Did not show any pathological symptom [NO ADVERSE EVENT]*	Not Applicable
	Case Narrative:		Report received from consumer on 30 Jun 2006: The child ingested accidentally 5-6 tablets of Zymafluor 0.25 mg (sodium fluoride) on 30 Jun 2006 at 7:50 am. The child received milk subsequently. On the same day at 4 pm, the child did not show any pathological symptom.					
[redacted]	Spontaneous Report	Female	**ZYMAFLUOR (NCH) / Unknown** 1 mg [1 mg-QD]	Oral	MAR-2006 to 08-JAN-2007	MAR-2006	Zymafluor 1mg instead of Zymafluor 0.25mg [OVERDOSE]	Not Applicable
	Patient Relevant History:		Historical Drug; [redacted] VITAMIN D Note: The child was treated with an unspecified Vitamin D compound from birth (on Feb 2005) to Mar 2006. Historical Drug; [redacted] FLUORIDE Note: The child was treated with an unspecified fluoride 0.25 mg compound from birth on (Feb 2005) to Mar 2006.					
	Case Narrative:		Consumer report received on 15 Jan 2007: a mother reported that her 23-month old child was prescribed Zymafluor 1 mg (sodium fluoride) instead of Zymafluor 0.25 mg from Mar 2006 to 08 Jan 2007. The paediatrician had accidentally prescribed the wrong dosage form Zymafluor 1 mg without additional Vitamin D from Mar 2006 to 08 Jan 2007. In Jan 2007, the child was diagnosed with a reduction of the growth curve of the child's body height. Treatment was discontinued on 08 Jan 2007. Outcome: unknow This follow-up combines information received on 22 jan 2007 and on 05 Feb 2007 from the mother of the consumer. The child was treated with an unspecified vitamin D compound and an unspecified fluoride 0.25mg compound from birth until Mar 2006. From Mar 2006 to 08 Jan 2007, the pediatrician had accidentally prescribed the wrong dosage form Zymafluor 1 mg without additional Vitamin D compound. The mother recognized the mistake in Jan 2007 and treatment was stopped on 08 Jan 2007. The mother specified that the diagnostics of a consulted senior children's specialist revealed no reduction of growth curve and a normal body height with regard to the age and family body height. But another consulted children's specialist recently detected an unclear "spotty bone structure in X-ray". Unspecified blood test and further diagnostics were planned. The outcome was unknown. Follow-up received on 27 Feb 2007: The father reported that the further diagnostics of a consulted senior children's specialist revealed no reduction of growth curve, a normal body height and that the detected "spotty bone structure in x-ray" was clinically not relevant. The detected structure in the x-ray was probably caused by a technical problem during the x-ray procedure and no pathological finding. The unspecified blood tests revealed no pathological findings. The final outcome of the event was complete recovery.					
Event System Organ Class: Skin and subcutaneous tissue disorders (1)								
[redacted]	Spontaneous Report		**ZYMAFLUOR (NCH) / Tablet** UNK [.25 mg-UNK]	Oral		MAY-2006 MAY-2006	Urticarial skin reaction / White wheals on alternating skin areas [URTICARIA] Reddened skin areas [ERYTHEMA]	Unknown
	Case Narrative:		Consumer report received on 06 Jun 2006: The 1.5-year-old child was treated with Zymafluor D 500 since birth and tolerated the compound well. In May 2006 the treatment was changed to Zymafluor 0.25 mg (sodium fluoride) and the child developed an urticarial skin reaction with reddened skin areas and white wheals on alternating skin areas. The reaction first occurred on the upper side of feet, then on the back. The patient's parents were advised to stop the treatment and to consult a physician. At the time of this report, the outcome was unknown.					

Total number of case entries printed in the Non-Medically Confirmed section: 15

Total number of cases printed in the Non-Medically Confirmed section: 15

[2] Non-Medically Confirmed.

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome

Total number of case entries printed: 15
Total number of cases printed: 15

[2] Non-Medically Confirmed.

Summary Tabulation

For All Products (Number of Events)

For the cases in this report

System Organ Class (SOC)	Preferred Term	Report Type: Spontaneous Report	Total
Gastrointestinal disorders	Diarrhoea	1	**1**
	SubTotal	**1**	**1**
General disorders and administration site conditions	No adverse event	12	**12**
	SubTotal	**12**	**12**
Injury, poisoning and procedural complications	Accidental drug intake by child	10	**10**
	Accidental overdose	4	**4**
	Incorrect dose administered	1	**1**
	Overdose	3	**3**
	SubTotal	**18**	**18**
Skin and subcutaneous tissue disorders	Erythema	1	**1**
	Urticaria	1	**1**
	SubTotal	**2**	**2**
Total		**33**	**33**

[2] Non-Medically Confirmed.

App 3.3.1 - Zymafluor - Aggregate summary tabulation HCP reports
Reporting Period: 01-Apr-2006 to 31-Jan-2009

		SR/LIT				SR/LIT	Grand
BODY_SYS	PREF_TERM	NS-L	NS-UL	S-UL	S-XX	Total	Total
Blood and lymphatic system disorders	Bone marrow failure			1		1	1
	Erythropoiesis abnormal				1	1	1
	Pancytopenia			1		1	1
	Thrombocytopenia				1	1	1
Blood and lymphatic system disorders Total				**2**	**2**	**4**	**4**
Eye disorders	Dark circles under eyes		1			1	1
Eye disorders Total			**1**			**1**	**1**
Gastrointestinal disorders	Abdominal pain		1			1	1
	Abdominal pain upper	1				1	1
	Diarrhoea		1			1	1
	Flatulence		1			1	1
	Fluorosis dental		1	1		2	2
	Gastritis		1			1	1
	Oedema mouth		1			1	1
	Stomatitis		1			1	1
	Tongue discolouration		1			1	1
	Tooth discolouration		4			4	4
	Vomiting	1				1	1
Gastrointestinal disorders Total		**2**	**12**	**1**		**15**	**15**
General disorders and administration site conditions	Calcinosis		1			1	1
	Inflammation		1			1	1
	Malaise		1			1	1
	No adverse event	11				11	11
	Oedema mucosal		1			1	1
	Pyrexia		1	1		2	2
General disorders and administration site conditions Total		**11**	**5**	**1**		**17**	**17**
Injury, poisoning and procedural complications	Accidental drug intake by child	16				16	16

App 3.3.1 - Zymafluor - Aggregate summary tabulation HCP reports
Reporting Period: 01-Apr-2006 to 31-Jan-2009

BODY_SYS	PREF_TERM	SR/LIT NS-L	SR/LIT NS-UL	SR/LIT S-UL	SR/LIT S-XX	SR/LIT Total	Grand Total
	Accidental overdose	12				12	12
	Drug exposure during pregnancy	2				2	2
	Fracture			1		1	1
	Incorrect dose administered	3				3	3
	Overdose	1				1	1
Injury, poisoning and procedural complications Total		**34**		**1**		**35**	**35**
Investigations	Biopsy bone abnormal		1			1	1
	Bone density decreased			1		1	1
	Fluoride increased		1			1	1
	Neutrophil count abnormal				1	1	1
Investigations Total			**2**	**1**	**1**	**4**	**4**
Metabolism and nutrition disorders	Hypovitaminosis		1			1	1
Metabolism and nutrition disorders Total			**1**			**1**	**1**
Musculoskeletal and connective tissue disorders	High turnover osteopathy		1			1	1
	Osteoporosis		2			2	2
Musculoskeletal and connective tissue disorders Total			**3**			**3**	**3**
Nervous system disorders	Dysgeusia		1			1	1
	Tremor		1			1	1
Nervous system disorders Total			**2**			**2**	**2**
Psychiatric disorders	Crying		2			2	2
	Nervousness		1			1	1
	Restlessness		1			1	1
	Stress		1			1	1
Psychiatric disorders Total			**5**			**5**	**5**
Respiratory, thoracic and mediastinal disorders	Cough		1			1	1
	Pharyngeal erythema		1			1	1

App 3.3.1 - Zymafluor - Aggregate summary tabulation HCP reports
Reporting Period: 01-Apr-2006 to 31-Jan-2009

		SR/LIT				SR/LIT	Grand
BODY_SYS	PREF_TERM	NS-L	NS-UL	S-UL	S-XX	Total	Total
Respiratory, thoracic and mediastinal disorders Total			**2**			**2**	**2**
Skin and subcutaneous tissue disorders	Alopecia		1			1	1
	Hyperhidrosis		1			1	1
	Hyperkeratosis		1			1	1
	Nail discolouration		1			1	1
	Nail disorder		1			1	1
	Nail dystrophy		1			1	1
Skin and subcutaneous tissue disorders Total			**6**			**6**	**6**
Vascular disorders	Pallor		2			2	2
Vascular disorders Total			**2**			**2**	**2**
Grand Total		47	41	6	3	97	97

App 3.3.2 - Zymafluor - Aggregate summary tabulation non-HCP reports
Reporting Period: 01-Apr-2006 to 31-Jan-2009

		SR/LIT		SR/LIT Total	Grand Total
BODY_SYS	PREF_TERM	NS-L	NS-UL		
Gastrointestinal disorders	Diarrhoea	1		1	1
Gastrointestinal disorders Total		**1**		**1**	**1**
General disorders and administration site conditions	Adverse drug reaction		1	1	1
	Discomfort		1	1	1
	No adverse event	12		12	12
General disorders and administration site conditions Total		**12**	**2**	**14**	**14**
Injury, poisoning and procedural complications	Accidental drug intake by child	10		10	10
	Accidental overdose	5		5	5
	Incorrect dose administered	1		1	1
	Intentional drug misuse		2	2	2
	Overdose	4		4	4
Injury, poisoning and procedural complications Total		**20**	**2**	**22**	**22**
Skin and subcutaneous tissue disorders	Erythema	1		1	1
	Hyperhidrosis		1	1	1
	Rash	1		1	1
	Urticaria	1		1	1
Skin and subcutaneous tissue disorders Total		**3**	**1**	**4**	**4**
Grand Total		36	5	41	41

App 3.4.1 Zymafluor cumulative summary tabulation HCP reports

For ZYMAFLUOR (NCH) (Number of Events)

For the Period 01-Jan-1900 Through 31-Dec-2008

Advanced Condition used in this report:

Advanced Condition: NCH_PSUR_CUMULATIVE_SUMTAB_HCP (Created by [redacted] C
Selection Criteria:
Case Report Type equal to Clinical Trial
Advanced Condition NCH_PSUR_CUMULATIVE_SUMTAB_HCP is overwritten by the following SQL statement:
SELECT DISTINCT cm.case_id FROM case_master cm, case_product cp, case_assess ca, (SELECT DISTINCT case_id, MAX(Hcp_Flag) Hcp_flag FROM case_reporters GROUP BY case_id) cr , case_dose_regimens cdr WHERE cm.case_id = cp.case_id AND cm.case_id = cr.case_id and cr.hcp_flag = 1 AND cm.case_id = ca.case_id (+) AND cm.state_id > 1 AND cdr.case_id(+) = cp.case_id AND cdr.seq_num(+)= cp.seq_num AND (UPPER(cp.co_drug_code) like 'H-ZF+%' or UPPER(cp.co_drug_code) like 'H-T05480+%') AND cp.drug_type = 1 AND (cm.rpt_type_id IN (1,3) OR (cm.rpt_type_id = 11 AND ca.agent_suspect = 1)) AND ca.SERIOUSNESS = 1 and ca.listedness = 2 AND (TRUNC(cm.create_time) between TO_DATE('01-JAN-1900', 'DD-MON-YYYY') and TO_DATE('31-Jan-2009', 'DD-MON-YYYY')) AND cm.case_id NOT IN (SELECT case_id FROM case_classifications WHERE classification_id IN [redacted] B

App 3.4.1 Zymafluor cumulative summary tabulation HCP reports

For ZYMAFLUOR (NCH) (Number of Events)

For the Period 01-Jan-1900 Through 31-Dec-2008

System Organ Class (SOC)	Preferred Term	Report Type		
		Literature Case	Spontaneous Report	**Total**
Blood and lymphatic system disorders	Bone marrow failure	0	1	**1**
	Erythropoiesis abnormal	0	1	**1**
	Pancytopenia	0	1	**1**
	Thrombocytopenia	0	1	**1**
	SubTotal	**0**	**4**	**4**
Cardiac disorders	Cyanosis	0	1	**1**
	SubTotal	**0**	**1**	**1**
Gastrointestinal disorders	Fluorosis dental	0	1	**1**
	Tooth discolouration	0	1	**1**
	Vomiting	0	1	**1**
	SubTotal	**0**	**3**	**3**
General disorders and administration site conditions	Asthenia	0	1	**1**
	Pyrexia	0	1	**1**
	SubTotal	**0**	**2**	**2**

App 3.4.1 Zymafluor cumulative summary tabulation HCP reports

For ZYMAFLUOR (NCH) (Number of Events)

For the Period 01-Jan-1900 Through 31-Dec-2008

System Organ Class (SOC)	Preferred Term	Report Type		
		Literature Case	Spontaneous Report	**Total**
Injury, poisoning and procedural complications	Accidental overdose	0	1	**1**
	Fracture	1	0	**1**
	Incorrect dose administered	0	1	**1**
	Multiple drug overdose accidental	0	1	**1**
	SubTotal	**1**	**3**	**4**
Investigations	Biopsy bone abnormal	1	0	**1**
	Bone density decreased	1	0	**1**
	Fluoride increased	1	0	**1**
	Neutrophil count abnormal	0	1	**1**
	SubTotal	**3**	**1**	**4**
Metabolism and nutrition disorders	Hypercalcaemia	0	1	**1**
	SubTotal	**0**	**1**	**1**

App 3.4.1 Zymafluor cumulative summary tabulation HCP reports

For ZYMAFLUOR (NCH) (Number of Events)

For the Period 01-Jan-1900 Through 31-Dec-2008

System Organ Class (SOC)	Preferred Term	Report Type		
		Literature Case	Spontaneous Report	**Total**
Musculoskeletal and connective tissue disorders	High turnover osteopathy	1	0	**1**
	Osteoporosis	1	0	**1**
	SubTotal	**2**	**0**	**2**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lymphoma	0	1	**1**
	SubTotal	**0**	**1**	**1**
Nervous system disorders	Loss of consciousness	0	1	**1**
	SubTotal	**0**	**1**	**1**
Respiratory, thoracic and mediastinal disorders	Cough	0	1	**1**
	Dyspnoea	0	1	**1**
	SubTotal	**0**	**2**	**2**
Skin and subcutaneous tissue disorders	Erythema multiforme	0	1	**1**
	SubTotal	**0**	**1**	**1**

App 3.4.1 Zymafluor cumulative summary tabulation HCP reports

For ZYMAFLUOR (NCH) (Number of Events)

For the Period 01-Jan-1900 Through 31-Dec-2008

System Organ Class (SOC)	Preferred Term	Report Type		
		Literature Case	Spontaneous Report	**Total**
Vascular disorders	Pallor	0	1	**1**
	SubTotal	**0**	**1**	**1**
Total		**6**	**21**	**27**

App 3.4.2 ZymaFluor cumulative summary tabulation non-HCP reports

For All Products (Number of Events)

For the Period 01-Jan-1900 Through 31-Jan-2009

Advanced Condition used in this report:

Advanced Condition: NCH_PSUR_CUMULATIVE_SUMTAB_NOHCP (Created by [redacted] C

Selection Criteria:

Case Report Type equal to Clinical Trial

Advanced Condition NCH_PSUR_CUMULATIVE_SUMTAB_NOHCP is overwritten by the following SQL statement:

SELECT DISTINCT cm.case_id FROM case_master cm, case_product cp, case_assess ca, (SELECT DISTINCT case_id, MAX(Hcp_Flag) Hcp_flag FROM case_reporters GROUP BY case_id) cr , case_dose_regimens cdr WHERE cm.case_id = cp.case_id AND cm.case_id = cr.case_id and cr.hcp_flag <> 1 AND cm.state_id > 1 AND cm.case_id = ca.case_id (+) AND cdr.case_id(+) = cp.case_id AND cdr.seq_num(+)= cp.seq_num

AND (UPPER(cp.co_drug_code) like 'H-ZF+%'

or UPPER(cp.co_drug_code) like 'H-T05480+%'

)

AND cp.drug_type = 1 AND (cm.rpt_type_id IN (1,3) OR (cm.rpt_type_id = 11 AND ca.agent_suspect = 1)) AND ca.SERIOUSNESS = 1 and ca.listedness = 2 AND (TRUNC(cm.create_time) between TO_DATE('01-JAN-1900', 'DD-MON-YYYY') and TO_DATE('31-Jan-2009', 'DD-MON-YYYY')) AND cm.case_id NOT IN (SELECT case_id FROM case_classifications WHERE classification_id IN (

[redacted]

B

App 3.4.2 ZymaFluor cumulative summary tabulation non-HCP reports

For All Products (Number of Events)

For the Period 01-Jan-1900 Through 31-Jan-2009

System Organ Class (SOC)	Preferred Term	Report Type: Spontaneous Report	**Total**
Gastrointestinal disorders	Tooth discolouration	1	**1**
	Tooth disorder	1	**1**
	SubTotal	**2**	**2**
Total		**2**	**2**