Fluoride toothpaste

1. Summary statement of the proposal for inclusion, change or deletion.

A modification to the existing entry for "sodium fluoride" in group 27 is requested to move it to a new category "30. Dental medicines" and a subgroup "30.1. Medicines for dental caries".

This application form relates to the change with regard to the entry for "sodium fluoride". The request is to move the existing entry (with wording as before) to the new proposed subgroup "30.1. Medicines to prevent and treat dental caries"; and to add a new entry for "fluoride toothpaste - 1000-1500ppm fluoride (any type)" (for EML and EMLc).

The rationale for the modification and addition of a new category for dental medicines and medical devices is grounded in the significant burden of oral diseases, particularly untreated dental caries. Oral diseases are major public health problems in all countries worldwide. Dental caries is the most common disease of mankind, affecting about 530 million children (deciduous teeth) and 2.3 billion adolescents and adults (permanent teeth).[9; 22]

Twice daily use of fluoride toothpaste for toothbrushing is an effective way to prevent dental caries among infants, children, adults and seniors. Extensive clinical trials over the last 60 years have shown that fluoride toothpaste delivers fluoride safely and is effective in preventing caries. The recommended concentration in toothpaste is between 1000 and 1500 ppm for all age groups.

Adequate topical use of fluoride has a beneficial effect on oral health in both children and adults. Fluoride prevents caries by several different actions. When present in saliva and dental plaque constantly and at low concentrations, fluoride delays the demineralization and hastens the remineralization of tooth enamel lesions. Fluoride also interferes with glycolysis, the process by which cariogenic bacteria metabolize sugars to produce acid. In addition, fluoride has a bactericidal action on cariogenic and other bacteria.[35]

There is no risk of acute fluoride toxicity from ingestion of fluoride toothpaste by young children, because the amount necessary to reach the dose probably toxic (DPT = 5.0 mg F/kg body weight) is very high; in fact, no cases have been reported in the literature. Fluoride toothpaste is one of the possible risk factors for dental fluorosis based on amount of toothpaste dispensed, amount ingested, age, and frequency and duration of use. Evidence shows that if at all the resulting levels of fluorosis are mild and do not affect the quality of life of children. Current recommendations for young children therefore suggest a "smear/rice sized" (for children below 3 years) and "pea sized" amount for young children. Limitation of package size and maximum fluoride content for a single unit and supervision of children to avoid ingestion the toothpaste slurry are the key risk mitigation measures recommended.[35]

Even though fluoride toothpaste is widely available in high-income countries, it is not universally accessible and affordable to populations in middle and low-income countries. Fluoride toothpaste is recommended for everyone at any age as part of daily personal hygiene behaviour, but only about 1.5 billion people are estimated to use it regularly.[7] Fluoride toothpaste is highly cost-effective and a unique public health intervention that combines cleaning of teeth and gums with a caries-preventive effect. There is no other product or intervention with a similar function. For this reason, fluoride toothpaste is considered the most rational way of fluoride use.

All these aspects combined make toothbrushing with fluoride toothpaste a significant public health approach in addressing the high burden of preventable caries across populations worldwide. Apart from dietary interventions through reduced intake of sugars, using fluoride toothpaste is the only self-care intervention that allows people to influence their caries incidence and severity.

2. Relevant WHO technical department and focal point (if applicable).

Dr Benoit Varenne, Dental Officer, Oral Health Programme, Noncommunicable Diseases Department, Division of UHC/Communicable and Noncommunicable Diseases

3. Name of organization(s) consulted and/or supporting the application.

WHO Collaborating Center Quality Improvement & Evidence-based Dentistry (WHO CC USA-429), College of Dentistry, New York University, New York, USA

Department of Dentistry, Radboud University Medical Centre, Nijmegen, The Netherlands

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

A01A: Stomatological preparations
A01AA: Caries prophylactic agents
This group comprises all types of fluoride preparations (tablets, gargles, toothpastes, chewing-gum etc.).

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Modification of the existing entry "sodium fluoride" in group 27 "vitamins and minerals" on the EML is sought. It is requested to modify the entry as follows:

1. Establish a new category on the EML "30. Dental Preparations"

2. To add within the new category "30.1. Medicines to prevent and manage dental caries"

3. Move the existing entry "sodium fluoride" to the new category 30.1. without changes to the specifications

4. Add an additional entry in new category 30.1: fluoride toothpaste.

Suggested new entry for EML & EMLc: Fluoridated toothpaste : paste, cream or gel containing between 1000 and 1500 ppm fluoride (any type)

ISO11609 (2017)[12] defines toothpaste as any semi-solid (paste, cream, gel) substance or combination of substances specially prepared for the public for hygiene of the accessible surfaces of teeth and surrounding tissues containing common constituents such as abrasives, humectants, binders, surfactants, flavourings, fluorides and other agents for oral health benefits. This covers the dual nature of fluoride toothpaste as a medicine (or medical device, medicinal product) and as a cosmetic product. Toothpaste without fluoride content within the recommended dosage margins should not be part of the EML.

WHO (2019) states that "fluoridated toothpastes containing between 1000 and 1500 ppm fluoride is the standard recommended by WHO as a public oral health measure for the prevention of caries."[18; 35]

A high-fluoride containing toothpaste variant exists with 2800ppm or 5000ppm for toothbrushing. It is indicated for individuals at high-risk of caries, for root dentine caries control or for supervised community settings (i.e. in schools). This application focuses on the standard concentration for daily use.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

TBC Fluoridated toothpaste: paste, cream or gel containing between 1000 and 1500 ppm fluoride (any type)

7. Treatment details (requirements for diagnosis, treatment and monitoring).

Brushing teeth with a fluoride toothpaste twice daily is a preventive lifelong hygiene behavior that is universally recommended to everyone and all age groups starting as soon as teeth erupt. Using fluoride toothpaste is not depending on the diagnosis of caries – for those without caries it helps to reduce incidence of the disease, for those with caries it helps to slow the disease progression and reduces incidence and severity of new cavities.

The report of a WHO Expert Committee on Oral Health Status and Fluoride Use (WHO TRS846) "Fluorides and oral health" (1994)[36] details evidence for various delivery forms of fluorides, their respective dosage, risks and side-effects (including their monitoring). Since then they have been complemented by evolving science and consensus as documented in WHO and WHO-led consensus documents,[18; 35; 37]} Cochrane reviews,[13; 30; 31] recommendations and clinical guidelines from CDC[5] and other major public health/professional organizations.[1; 24; 44]

Recommendations can be summarized as follows:

- Toothpaste should contain at least 1000ppm (w/w; 1000 mg F/kg = 1.0 mg F/g) of fluoride and no more than 1500ppm of fluoride.
- Special formulations for children are not recommended due to lack of evidence of a caries-preventive effect for toothpaste containing less than 1000ppm fluoride.[31]
- Children less than 3 years old: Begin brushing as soon as teeth erupt using no more than a smear of the size of a rice grain of regular (adult) fluoride toothpaste. Parents/caregiver brush the teeth 2x/day or as directed by a dentist or physician; supervision is required to ensure that toothpaste slurry is not swallowed but spat out without subsequent rinsing.

- Children 3-6 years should: Brush teeth with a pea-sized amount of regular (adult) toothpaste. Parents/caregiver brush the teeth 2x/day or as directed by a dentist or physician; supervision is required to ensure that toothpaste slurry is not swallowed but spat out without subsequent rinsing.
- Children older than 6 years – all other ages & adults: Brush teeth 2x/day with a pea-sized amount of fluoride toothpaste without subsequent rinsing.

ISO11609 (2017)[12], among other aspects, specifies labeling requirements and asks for age-specific usage instructions to be printed on the package.

8. Information supporting the public health relevance.

Epidemiological information on disease burden / public health need:

The Global Burden of Disease Study 2017 estimated that oral diseases affect close to 3.5 billion people worldwide, with caries of permanent teeth being the most common condition. Globally, it is estimated that 2.3 billion people suffer from caries of permanent teeth and more than 530 million children suffer from caries of primary teeth.[9] The majority of caries remains untreated. The caries burden is hugely unequal across populations within and between countries, with a clear socio-economic gradient showing higher disease burden in deprived and disadvantaged populations that at the same time have less access to care, including prevention.[21] Caries is a disease of all age groups with an onset in early childhood and continued increase over the life-course. Most significant increases in incidence are observed in adolescent age groups.

A high prevalence and severity of untreated dental caries is a co-factor for low BMI and stunting; it also leads to significant absenteeism in school and workplaces. Good oral health is also vital for healthy ageing, playing a crucial role with regard to nutrition.

Assessment of current use of fluoride toothpaste

The use of fluoride toothpaste is a public health intervention designed for self-care as part of daily toothbrushing for all age groups throughout the life course. Assessment of current usage is challenging, as it is dependent on personal oral hygiene habits, and affordability/availability of fluoride toothpaste to the individual.

Usage has been assessed in selected populations and sub-groups using self-reported surveys which tend to over-report. Reported rates of toothbrushing with fluoride toothpaste range from about 60% of children in the US[27], 70% across all age groups in Portugal,[26] 50% (Lithuania), and 80% (Sweden) among children in 20 European countries.[11] Similar rates are reported from the Global School-based Health Survey.[19; 25] In Burkina Faso, only 9% of 12-year-olds and 18% of 35-44-year-olds reported use of fluoride toothpaste; in rural China only 2% of children use fluoride toothpaste.[8; 29] Most of these studies only report toothbrushing behavior and do not specifically ask for the use of fluoride toothpaste. Reliable data on usage in adults is not available. In the absence of publicly available sales information from manufacturers, the global usage of fluoride toothpaste has been estimated at around 1.5 billion people.[7]

The low affordability of fluoride toothpaste is a significant usage challenge, particularly for poor population segments in LMIC.[10] WHO conducted a survey on affordability of fluoride toothpaste in the context of the upcoming WHO Global Oral Health Report (to be released in May 2021), analyzing data from 80 countries and using the WHO HAI methodology. The survey documented a high variability of prices for fluoride toothpaste and high cost particularly for the poorest 15% of the population in countries of Sub-Saharan Africa, parts of South and Southeast Asia and the Pacific Islands. In these countries the cost of the annual supply of fluoride toothpaste per person would even lead to catastrophic health expenditure.

Population impact of using fluoride toothpaste

Globally, prevalence and incidence of untreated caries have remained almost unchanged between 1990 and 2017[9], while the total number of individuals affected has significantly increased due to population demographics, particularly in LMIC. At the same time HIC observed a strong and consistent decrease of caries burden which coincides with the market introduction of fluoride toothpaste in the early 1960s.[23] Increased usage and affordability of fluoride toothpastes are expected to have similar impact on current populations in LMIC.[32] WHO global and regional policy documents and implementation manuals emphasize the importance of fluoride toothpaste and prioritize measures to improve quality, accessibility and affordability. [38; 41–43]

9. Review of benefits: summary of evidence of comparative effectiveness.

Available Cochrane and other systematic reviews show strong evidence for effectiveness of fluoride toothpaste in children, including early childhood caries, and adults:[6; 13–15; 30; 31; 39; 40]

- Primary and permanent teeth: "The are benefits of using fluoride toothpaste at certain strengths to prevent tooth decay when compared with non-fluoride toothpaste. The stronger the fluoride concentration, the more decay is prevented"
- The preventive fraction in the permanent dentition using a 1500ppm fluoride toothpaste was 24% in 70 studies summing observations from 42,300 children over three years (preventive fraction is the difference in mean caries increments between the treatment and control groups expressed as a percentage of the mean increment in the control group).[13]
- The effect increased with higher baseline caries levels, higher fluoride concentration in the toothpaste, higher frequency of use and supervised toothbrushing (higher compliance).[30]
- When compared with mouthrinse and gels, fluoride toothpastes have similar effectiveness for the prevention of dental caries in children. Acceptance is likely to be greater for fluoride toothpaste.[14]

10. Review of harms and toxicity: summary of evidence of safety.

The harms and toxicity of fluoride toothpaste have been analyzed by several high-quality Cochrane and other systematic reviews.[13; 30; 31; 34] A recent WHO report reviewed the state of evidence.[35] In summary, harms and toxicity of fluoride toothpaste are related to either toxicity through ingestion (unintentional/intentional) and to the risk of dental fluorosis (a hypomineralization of the enamel caused by ingestion of excessive fluoride levels during tooth formation).

- The risk of acute fluoride toxicity occurs when young children ingest large amounts of toothpaste. There is no report in the literature of such events. The U.S. FDA regulates that the total amount of fluoride in any package sold over-the-counter to not exceed more than 276 mg to prevent problems if the whole tube is swallowed.
- For the same reasons ISO11609 limits the maximum fluoride content for a single size container to 300mg, unless a larger container is used in the supervised community context and not sold over-the-counter.
- While the main sources of ingested fluoride include water from areas high in natural fluoride concentration, food or certain teas, there is a risk of dental fluorosis that is related to ingestion of toothpaste by young children during the phase of tooth development (either of the deciduous or permanent teeth)[34]
- Use of pea-size amount was not associated with mild to moderate fluorosis, the concentration of fluoride in the toothpaste was not associated with fluorosis risk.[20; 34; 35]

Other side effects of fluoride toothpaste have not been reported (apart from reactions to other ingredients of toothpaste formulations such as adverse reactions to surfactants).

Mitigation measures include recommendations and package labelling requesting supervision of children while brushing, limiting the amount of toothpaste used (pea size) and the limitation of total fluoride content in a single container.[12; 35]

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

As a personal preventive and hygiene activity, the cost of fluoride toothpaste and toothbrushes is an out-of-pocket expense, apart from limited community programmes for children where toothpaste cost is otherwise covered. Prices for toothpaste vary significantly between available brands, fluoride compounds and package sizes; as well as between countries. In a number of countries taxes and import duties are markedly increasing consumer cost, leading to considerations around manufacturing an affordably priced toothpaste for LMIC.[4; 10; 28]

Cost-effectiveness of fluoride toothpaste is very good, with costs per usage (one toothbrushing event) of <0.05$USD or annual supply per person between 0.50 and 36.50$USD[17; 33] All school-based oral health programmes include some form of supervised or unsupervised toothbrushing with fluoride toothpaste. Several studies demonstrated the high cost-effectiveness of such an approach.[2; 3; 16]

Cost-effectiveness remains high in comparison with other fluoride interventions, though there is no other intervention that combines cleaning of teeth and gums with caries-preventive effects. Toothbrushing without fluoride toothpaste has no caries-preventive effect.[17]

12. Summary of regulatory status and market availability of the medicine.

It is safe to assume that fluoride toothpaste is available in every country worldwide. In most countries fluoride toothpaste is regulated as a cosmetic product (or medical device or medicinal product see above mentioned link) for products containing up to 1500ppm fluoride. Toothpaste with higher fluoride concentrations (up to 5000ppm fluoride) are often regulated as medicines or medical products and require a prescription.

International standards for testing, quality, labeling and consumer protection are provided by ISO11609 (2017)[12], which are complemented by regional or national standards (see Annex).

European Union regulation specifies labeling for dosage and strengths of 21 different fluoride compounds in fluoride toothpaste:

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32013R0344&from=EN

The active ingredient must be listed. In addition, "For any toothpaste with compounds containing fluoride in a concentration of 0.1 to 0.15% calculated as F unless it is already labeled as contra-indicated for children (e.g. "for adult use only") the following labelling is obligatory: "Children of 6 years and younger use a pea-sized amount for supervised brushing to minimize swallowing. In case of intake of fluoride from other sources consult a dentist or doctor."

The 21 fluoride compounds are: nicomethanol hydrofluoride, magnesium fluoride, ammonium monofluorophosphate, sodium monofluorophosphate, potassium monofluorophosphate, calcium monofluorophosphate, sodium fluoride, potassium fluoride, ammonium fluoride, aluminium fluoride, stannous fluoride, cetylamine hydrofluoride, 3(N-Hexadecyl-N-2-hydroxyethylammonio) propylbis (2-hydroxyethyl) ammonium difluoride, N,N',N'-tris(polyoxyethylene)-N-hexadecylproyplenediamine dihydrofluoride, octadecenyl-ammonium fluoride, sodium fluorosilicate, potassium fluorosilicate, ammonium fluorosilicate, magnesium fluorosilicate, nicomethanol hydrofluoride, magnesium fluoride.

In the U.S., all anti-caries fluoride drug products for over-the-counter human use are regulated by U.S Food and Drug Administration (FDA) under CFC 0 Code of Federal regulations Title 21 (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=355&showFR=1) The FDA has summarized its rulemaking history of over-the-counter anti-caries products, including fluoride toothpaste, on the following website: https://www.fda.gov/drugs/status-otc-rulemakings/rulemaking-history-otc-anticaries-drug-products

The accepted active ingredients are:

- Sodium fluoride (NaF). Dentifrices containing 850-1,150 ppm (parts per million of fluoride in the formulation.
- Sodium monofluorophosphate (MFP). Dentifrices containing 850-1,150 ppm and 1,500 ppm. Based on molecular weight, the percent fluoride in (2) and (1) are different.
- Stannous fluoride (SnF_2). Dentifrices containing 850-1,150 ppm.

To avoid acute toxicity from ingestion, packages should not contain more than 276 mg of total fluoride. There are restrictions on labeling and warnings regarding direct ingestion. Lower fluoride formulations are not authorized for use in the U.S. but are sold in other parts of the world, despite evidence for a lack of anti-caries efficacy.

ISO11609 (2017)[12] also limits the maximum package size for consumer packaging of fluoride toothpaste to 300 mg.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

The International Pharmacopoeia 2019

Sodium fluoride: https://apps.who.int/phint/pdf/b/6.1.328.Sodium-fluoride-(Natrii-fluoridum).pdf

The United States Pharmacopoeia

Part 335 – anticaries drug products for over-the-counter human use (A - general provisions/B – active ingredients/ C - labeling/ D – testing procedures

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Annex

Selected standards and regulations for fluoride toothpaste

Standard/Regulation	Total fluoride (TF)	Total Soluble Fluoride (TSF)
ISO 11609:2017	Not greater than 1,500 ppm F	Not specified
European Union (2009)	Not greater than 1,500 ppm F	Not specified
Mercosur (Argentina, Brazil, Paraguay, Uruguay and Venezuela) (2002)	Not greater than 1,500 ppm F	Not specified
Peru (2001)	Not greater than 1,500 ppm F	Toothpastes with 1000 - 1500 ppm F must have at least 600 ppm TSF for the year of production and 450 ppm until expiry. Toothpastes with 250 - 550 ppm F must provide at least 60% TSF until expiry.
ASEAN (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, and Vietnam) (2003)	Not greater than 1,500 ppm F	Not specified
Thailand (ASEAN country but with special exception)	Not greater than 1,100 ppm F	Not specified
Japan (2017)	Not greater than 1,500 ppm F (Previously not greater than 1,000 ppm F)	Not specified
India (2001)	Not greater than 1,000 ppm F	Not greater than 1,000 ppm TSF
South Africa (SANS 1302:2008)	Not greater than 1,500 ppm F	Not specified
East African Standard (Burundi, Kenya, Rwanda, Tanzania and Uganda) (EAS 187:2000)	SMFP: 850 - 1120 ppm F* Stannous fluoride: 900 -1120 ppm F Sodium fluoride: 900 - 1150 ppm F*	600 ppm TSF 108 - 500 ppm TSF* 403 - 600 ppm TSF*
United States Food and Drug Authority (2015)	850 - 1150 ppm F (for children ≥ 2 years 1500 ppm F (for children ≥ 6 years)	SMFP toothpastes with 850 to 1,150 ppm TF must contain at least 800 ppm TSF SMFP toothpastes with 1,500 ppm TF must contain at least 1275 ppm TSF Stannous fluoride toothpastes of 850 to 1,150 ppm TF must contain at least 700ppm TSF Sodium fluoride toothpaste with 850-1,150 ppm TF must contain at least 650ppm TSF
ADA (2016)	Total fluoride according ANSI/ADA Standard No.130 or ISO11609, 2010	At least 90% of the labelled amount of fluoride must be available in both fresh and aged samples. (Fresh samples = analysed within 1 month of formulation, aged samples = those at the effective end of their expiration period)