


		EMLc	ATC codes: A01AA01 A01AA04
Indication	Dental caries	ICD11 code: DA08.0	
Medicine type	Chemical agent		
List type	Core		
Formulations	Local > Dental > Paste: 1000 to 1500 ppm fluoride (any type) Local > Dental > Cream: 1000 to 1500 ppm fluoride (any type) Local > Dental > Gel: 1000 to 1500 ppm fluoride (any type) Local > Dental > Other: In other appropriate topical formulations		
EML status history	First added in 1979 (TRS 641) Changed in 1993 (TRS 850) Changed in 2005 (TRS 933) Changed in 2007 (TRS 950) Changed in 2021 (TRS 1035)		
Sex	All		
Age	Also recommended for children		
Therapeutic alternatives	The recommendation is for this specific medicine		
Patent information	Patents have expired in most jurisdictions Read more about patents . 		
Wikipedia	Fluoride 		
DrugBank	Sodium fluoride 		

Expert Committee recommendation

The Expert Committee noted that dental caries of permanent teeth affects an estimated 2.3 billion people worldwide and more than 530 million children suffer from caries of primary teeth. Inequalities throughout the life course and across populations in the low-, middle- and high-income countries were also noted, with the highest burden in countries with limited resources for caries prevention and control. The Expert Committee noted that the use of fluoride toothpaste reduces caries lesions by one quarter compared with non-fluoride toothpaste, according to cumulative data across studies. Despite fluoride toothpaste being a foundation of oral health prevention strategies, the Committee observed that the current listing for sodium fluoride in the EML and EMLc does not specify the form and concentration range of topical fluoride products used to prevent dental caries, specifying only “in any appropriate topical formulation”. The Committee considered that to provide the best guidance for selection of products for national EMLs, the Model Lists should include specific recommendations of the different formulation types and ideal concentrations of fluoride-containing preparations. The Expert Committee took into account that fluoridated toothpaste containing between 1000 ppm and 1500 ppm fluoride is the standard strength recommended by WHO as a public oral health measure to prevent caries. The Committee also considered that to prevent the risk associated with ingestion of toothpaste, limitation of package size and maximum fluoride content for a single unit with a well defined concentration range would be helpful. Furthermore, the Committee noted the risk of substandard toothpastes being marketed with low or nil concentration of fluoride. Specifying fluoride amount and concentration can help national authorities to develop standards for production and to implement quality-control actions to identify marketed toothpastes that do not meet recommended fluoride standards. The Committee also noted that additional fluoride sources (e.g. water supply) should be taken into consideration by countries. The Expert Committee recommended that the current listing for sodium fluoride be transferred from Section 27 (Vitamins and Minerals) to a new section of the EML and EMLc for dental preparations. The listing should be amended to “fluoride”, noting that topical fluoride-containing

preparations use fluoride in a variety of forms. Fluoride toothpaste is recommended for inclusion as a specifically defined formulation of fluoride (paste, cream or gel containing between 1000 ppm and 1500 ppm fluoride any type), because of its proven effectiveness in preventing dental caries and for better control of the quantity of fluoride contained in toothpaste. The Committee requested WHO to identify and define the alternative fluoride-containing formulations that are recommended for use in the prevention of dental caries so that these can be clearly indicated in the Model Lists in 2023 to provide clear guidance to countries. The Expert Committee recommended that the current listing for sodium fluoride be transferred from Section 27 (Vitamins and Minerals) to a new section of the EML and EMLc for dental preparations. The listing should be amended to “fluoride”, noting that topical fluoride-containing preparations use fluoride in a variety of forms. Fluoride toothpaste is recommended for inclusion as a specifically defined formulation of fluoride (paste, cream or gel containing between 1000 ppm and 1500 ppm fluoride any type), because of its proven effectiveness in preventing dental caries and for better control of the quantity of fluoride contained in toothpaste. The Committee requested WHO to identify and define the alternative fluoride-containing formulations that are recommended for use in the prevention of dental caries so that these can be clearly indicated in the Model Lists in 2023 to provide clear guidance to countries.

Background

Sodium fluoride tablets were first included on the EML in 1979 for use as a prophylactic measure against dental caries where water supplies are not fluoridated (1). In 1993, the listing was amended to accommodate other formulations. In 2005, a proposal to remove sodium fluoride was considered by the Expert Committee. In consideration of this proposal, the Committee noted that the efficacy of topical fluoride preparations in preventing dental caries was firmly established. The Committee also noted that the selection of a suitable fluoride preparation should take into account local circumstances, including the fluoride content of drinking-water. Fluoride tablets are no longer recommended because of the risk of fluorosis when they are used in excess. The Committee therefore recommended that sodium fluoride be retained on the Model List, but that the description be changed to “in any appropriate topical formulation” (2). In 2007, sodium fluoride was included in the first edition of the EMLc (3).

Public health relevance

The 2017 Global Burden of Disease Study estimated that oral diseases affect close to 3.5 billion people worldwide, with caries of permanent teeth being the most common condition. Globally, 2.3 billion people are estimated to suffer from caries of permanent teeth and more than 530 million children suffer from caries of primary teeth (4). Most caries are untreated. The caries burden is very unequal across populations within and between countries, with a clear socioeconomic gradient showing higher disease burden in deprived and disadvantaged populations who at the same time have less access to care, including preventive care (5). 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 associated with low body mass index and stunting; it also leads to considerable absenteeism in school and the workplace. 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 use is challenging as it is dependent on personal oral hygiene habits and affordability/availability of fluoride toothpaste to the individual. Use of fluoride toothpaste has been assessed in some populations and sub-groups using self-reported surveys which tend to over-report. Reported rates of toothbrushing with fluoride toothpaste vary: about 60% of children in the United States of America (6), 70% of all age groups in Portugal (7), 50% of children in Lithuania and 80% of children in Sweden (8). Similar rates are reported from the global school-based health survey (9,10). In Burkina Faso, only 9% of 12-year-old children and 18% of 35–44-year-old adults reported use of fluoride toothpaste (11), and in rural China only 2% of children use fluoride toothpaste (12). Most of these studies only report toothbrushing behaviour and do not specifically ask about the use of fluoride toothpaste. Reliable data on use of fluoride toothpaste in adults are not available. In the absence of publicly available sales information from manufacturers, the global use of fluoride toothpaste has been estimated at around 1.5 billion people (13). The low affordability of fluoride toothpaste is a significant obstacle to its use, particularly for poor populations in low- and middle-income countries (14). WHO conducted a survey on affordability of fluoride toothpaste for an upcoming WHO global oral health report, analysing data from 80 countries and using the WHO/Health Action International methodology. The survey documented a large variation in prices of fluoride toothpaste and high costs, particularly for the poorest 15% of the population in countries of sub-Saharan Africa, parts of south and south-east Asia and the Pacific Islands. In these countries, the cost of an annual supply of fluoride toothpaste per person would lead to catastrophic health expenditure. Globally, the prevalence and incidence of untreated caries changed little between 1990 and 2017 (4), while the total number of individuals affected significantly increased due to population

demographics, particularly in low- and middle-income countries. At the same time high-income countries observed a strong and consistent decrease in the caries burden, which coincided with the introduction of fluoride toothpaste to markets in the early 1960s (15). Increased use and affordability of fluoride toothpastes are expected to have similar effect on current populations in low- and middle-income countries (16). WHO global and regional policy documents and implementation manuals emphasize the importance of fluoride toothpaste and prioritize measures to improve quality, accessibility and affordability (17–20).

Benefits

The application presented a summary of available Cochrane and other systematic reviews as evidence for the effectiveness of fluoride toothpaste in children, including in prevention of early childhood caries, and adults. A 2019 Cochrane review of 94 studies published between 1955 and 2014 evaluated the effects of toothpastes of different fluoride concentrations (between 1000 ppm and 2800 ppm) in preventing dental caries in children, adolescents and adults (21). The review findings supported the benefits of using fluoride toothpaste for the prevention of caries compared with non-fluoride toothpaste. For fluoride concentration, a dose–response effect was observed in children and adolescents. In adults, a fluoride concentration of 1000 ppm or 1100 ppm was found to reduce caries compared with non-fluoride toothpaste. A 2003 Cochrane review and meta-analysis of 70 studies (42 300 participants) evaluated the effectiveness and safety of fluoride toothpastes in the prevention of dental caries in children. The main outcome of the studies was caries increment measured by the change in decayed, missing and filled tooth surfaces (D(M)FS) (22). The preventive fraction (the difference in mean caries increments between the treatment and control groups expressed as a percentage of the mean increment in the control group) in the permanent dentition using a 1500 ppm fluoride toothpaste was 24% (95% confidence interval (CI) 21 to 28%; $P < 0.0001$). For a population with a caries increment of 2.6 D(M)FS per year, 1.6 children would need to brush with a fluoride toothpaste over 3 years to prevent one D(M)FS. The effect of fluoride toothpaste increased with higher baseline caries levels, higher fluoride concentration, higher frequency of use and supervised toothbrushing. A 2004 Cochrane review of 12 studies compared the effectiveness of two topical fluoride treatments (e.g. toothpastes, mouth rinses, gels and varnishes) used together with one of the treatments alone (mainly toothpaste) when used for the prevention of dental caries in children (23). Compared to mouth rinses and gels, fluoride toothpastes had similar effectiveness for the prevention of dental caries in children. A systematic review and meta-analysis of eight clinical trials evaluated the effects of fluoride toothpastes on the prevention of dental caries in the primary dentition of preschool children (24). A significant reduction in caries was observed at surface, tooth and individual levels for standard fluoride toothpastes (1000–1500 ppm) compared with placebo or no intervention. The authors concluded that the use of standard fluoride toothpastes should be recommended for use by preschool children.

Harms

The harms and toxicity of fluoride toothpaste have been analysed by several high-quality Cochrane and other systematic reviews (21,22,25,26). A recent WHO report reviewed the state of the evidence (27). In summary, the harms and toxicity of fluoride toothpaste are related to either toxicity through ingestion (unintentional/intentional) and to the risk of dental fluorosis (the 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 are no reports in the literature of such events. The US Food and Drug Administration stipulates that the total amount of fluoride in any package sold over the counter must not be more than 276 mg to prevent problems if the whole tube is swallowed. For the same reasons, the International Organization for Standardization standard ISO11609 limits the maximum fluoride content of a single-size container to 300 mg unless a larger container is used in a supervised community context and not sold over the counter (28). While the main sources of ingested fluoride are water from areas with high concentrations of natural fluoride, food or certain teas, there is a risk of dental fluorosis from the ingestion of toothpaste by young children during tooth development (either of the deciduous or permanent teeth) (26). Use of a pea-size amount of fluoride toothpaste was not associated with mild to moderate fluorosis and the concentration of fluoride in toothpaste was also not associated with fluorosis risk (15,26,27). Other side-effects of fluoride toothpaste have not been reported apart from reactions to other ingredients of toothpaste formulations (e.g. surfactants). Measures to reduce the risk of fluorosis include recommendations and package labelling requesting supervision of children while brushing, limiting the amount of toothpaste used and the limitation of total fluoride content in a single toothpaste container (27,28).

Cost / cost effectiveness

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 of toothpaste vary considerably 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 low- and middle-income countries (14,36,37). Fluoride toothpaste is considered to be cost-effective, with costs per usage (one toothbrushing event) of less than US\$ 0.05 or annual supply per person between US\$ 0.50 and US\$ 36.50 (38,39). All school-based oral health programmes include some form of supervised or unsupervised toothbrushing with fluoride toothpaste. Several studies have demonstrated the high cost-effectiveness of such an approach (36,40,41). The cost-effectiveness of fluoride toothpaste is still higher than other fluoride interventions, although there is no other intervention that combines cleaning of teeth and gums with caries-preventive measures. Toothbrushing without fluoride toothpaste has no caries-preventive effect (38).

WHO guidelines

The 1994 WHO technical report on fluorides and oral health details evidence for various delivery forms of fluorides, their dosage, risks, side-effects and monitoring (29). Since then, the evidence has been complemented by evolving science and consensus as documented in other WHO and WHO-led documents (27,30,31), Cochrane systematic reviews (21,22,25), and recommendations and clinical guidelines from the US Centers for Disease Control and Prevention and other major public health and professional organizations (32–35). Their recommendations are summarized below. • Toothpaste should contain at least 1000 ppm of fluoride (w/w 1000 mg fluoride/kg = 1 mg fluoride/g) and no more than 1500 ppm of fluoride. • Special formulations for children are not recommended due to lack of evidence that toothpaste containing less than 1000 ppm fluoride prevents caries. • For children younger than 3 years, begin brushing as soon as teeth erupt using no more than a smear of fluoride toothpaste the size of a rice grain of regular (adult) toothpaste. Parents/caregivers should brush children's teeth twice a 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/caregivers should brush children's teeth twice a 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, adolescents and adults should brush teeth twice a day with a pea-sized amount of fluoride toothpaste without subsequent rinsing.

Availability

Fluoride toothpaste is available worldwide. In most countries, it is regulated as a cosmetic product (or medical device or medicinal product) for products containing up to 1500 ppm fluoride. Toothpastes with a higher fluoride concentration (up to 5000 ppm fluoride) are often regulated as medicines or medical products requiring a prescription.

Other considerations

European Union regulation (42) specifies labelling for dosage and strengths of 21 different fluoride compounds in fluoride toothpaste: 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-hexadecylpropylenediamine dihydrofluoride, octadecenyl-ammonium fluoride, sodium fluorosilicate, potassium fluorosilicate, ammonium fluorosilicate, magnesium fluorosilicate, nicomethanol hydrofluoride and magnesium fluoride. 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 labelled 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.'" In the USA, all anticaries fluoride drug products for over-the-counter human use are regulated by the US Food and Drug Administration under Code of Federal Regulations Title 21 (43). The accepted active ingredients are: • Sodium fluoride. Dentifrices containing 850–1150 ppm of theoretical total fluorine in the formulation. • Sodium monofluorophosphate. Dentifrices containing 850–1150 ppm and 1500 ppm of theoretical total fluorine. • Stannous fluoride. Dentifrices containing 850–1150 ppm of theoretical total fluorine. To avoid acute toxicity from ingestion, packages should not contain more than 276 mg of total fluoride. There are restrictions on labelling and warnings about direct ingestion. Lower fluoride formulations are not authorized for use in the USA but

are sold in other parts of the world, despite a lack of evidence that they prevent caries.

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