Fluoride

Section: 30. Dental medicines and preparations

EMLc | ATC codes: A01AA01 A01AA04

Indication	Dental caries ICD11 code: DA08.0
Medicine type	Chemical agent
List type	Core
Formulations	**Local > Dental > Gel:** 2500 to 12500 ppm fluoride (any type) **Local > Dental > Toothpaste, cream or gel:** 1000 to 1500 ppm fluoride (any type) **Local > Dental > Mouthrinse:** 230 to 900 ppm fluoride (any type) **Local > Dental > Varnish:** 22500 ppm fluoride (any type)
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) Changed in 2023 (TRS 1049)
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 acknowledged the large global burden of dental caries and noted the work undertaken by WHO in developing a global oral health action plan, in which a target has been set that 50% of countries will include essential dental preparations on the EML/EMLc in their national essential medicines lists by 2030. The Committee recalled the request of the 2021 Expert Committee for WHO to identify and define alternative fluoride-containing formulations for use in the prevention of dental caries. The Committee considered that the evidence presented in the applications for fluoride gel, mouthrinse and varnish supported the effectiveness and safety of these products in the prevention of dental caries. The Committee also noted that that school-based fluoride programmes had been shown to be a cost-effective public health intervention in some settings. The Expert Committee therefore recommended the inclusion of gel, mouthrinse and varnish as specific formulations of fluoride on the core list of the EML and EMLc for prevention of dental caries.

Background

Sodium fluoride tablets were initially added to EML in 1979 as a preventive measure against dental caries in areas without fluoridated water supplies. In 1993, the listing was modified to include other formulations. In 2005, there was a proposal to remove sodium fluoride tablets due to the established efficacy of topical fluoride in preventing dental caries. The 2005 Expert Committee considered local circumstances, including the fluoride content of

drinking water, and acknowledged the risk of fluorosis with excessive tablet use. Consequently, sodium fluoride was retained on the EML but with a revised description to specify “in any appropriate topical formulation”. In 2007, sodium fluoride was also included in the first edition of the EMLc. In 2021, in consideration of an application proposing the addition of fluoride toothpaste to the EML and EMLc, the Expert Committee noted that the current listing for sodium fluoride did not specify the form and concentration range of topical fluoride products used to prevent dental caries. 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 Committee recommended that the listing for sodium fluoride be transferred to a new section of the Model Lists for dental preparations, and the listing be amended to “fluoride”, noting that topical fluoride-containing preparations use fluoride in a variety of forms. Fluoride toothpaste, containing between 1000 and 1500 ppm fluoride of any type was recommended for addition, and the Committee requested WHO to identify and define the alternative fluoride-containing formulations recommended for use in the prevention of dental caries so that these could be clearly indicated in the Model Lists in 2023 to provide clear guidance for countries (1).

Public health relevance

The WHO global oral health status report, using the latest available data of the Global Burden of Disease Study 2019, estimates that oral diseases affect close to 3.5 billion people worldwide. Dental caries is the most widespread oral disease with more than 2.5 billion untreated cases. This includes more than 2 billion estimated cases of caries in permanent teeth (global average prevalence of 29%) and 514 million estimated cases of caries in primary (deciduous) teeth (global average prevalence of 43%). Among the 194 WHO Member States, 134 have prevalence figures greater than 40% for caries in primary teeth. More than three quarters of cases of untreated caries in teeth are found in middle-income countries. Over the past 30 years, cases of untreated caries have increased and surpassed the demographic population growth during the same period (2). Untreated dental caries may cause pain and infection, and may lead to systemic infections requiring hospitalization and complex treatment. The high prevalence and severity of untreated dental caries in children can contribute to low body mass index and stunting (3–5). Additionally, dental caries result in significant absenteeism in schools and workplaces (6,7). Good oral health is essential for healthy ageing (8). The burden of dental caries varies significantly across populations within and between countries, with a clear socioeconomic gradient showing higher disease burden in deprived and disadvantaged communities, who also have limited access to prevention and oral health services (2,9). Caries affects people throughout their lives, with varying patterns of burden across age groups – starting in early childhood, increasing notably in adolescence and continuing to rise in adulthood (10).

Benefits

Fluoride gel A 2015 Cochrane systematic review of 28 randomized controlled trials (9140 participants) assessed the effectiveness of fluoride gels for preventing dental caries in children and adolescents (11). The primary outcome measure was caries increment measured by the change from baseline at the nearest increment to 3 years in decayed, missing/extracted and filled tooth surfaces in permanent and primary teeth. From the meta-analysis of fluoride gel compared with placebo or no treatment, fluoride gel significantly reduced decayed, missing and filled tooth surfaces in permanent teeth (prevented fraction (PF) 28%, 95% confidence interval (CI) 19% to 36%; 25 randomized controlled trials, 8479 participants, moderate quality evidence) and in primary teeth (PF 20%, 95% CI 1% to 38%; three randomized controlled trials, 1254 participants, low quality evidence). The effects showed no dependency on baseline caries level, or exposure to other fluoride sources, or to application features such as the method or frequency of gel application or fluoride concentration. The relative effect was not dependent on length of follow-up, whether prophylaxis was undertaken before application of the gel, or according to drop-out rate. Fluoride mouthrinse A 2016 Cochrane systematic review of 37 randomized trials (15 813 participants) assessed the effectiveness of fluoride mouthrinse for preventing dental caries in children and adolescents (12). Most participants received a mouthrinse formulated with sodium fluoride on either a daily or weekly/fortnightly basis and at two main strengths, 230 or 900 ppm fluoride. Meta-analysis found that fluoride mouthrinse significantly reduced decayed, missing and filled tooth surfaces in permanent teeth (PF 27%, 95% CI

23% to 30%; 35 randomized controlled trials, 15 305 participants, moderate quality evidence). No significant association was found between estimates of effect and baseline caries severity, exposure to other fluorides, rinsing frequency or fluoride concentration. A 2020 systematic review and network meta-analysis of nine controlled clinical trials (4030 participants) assessed the effect of topical fluoride preparations in preventing root caries (13). Daily use of 0.2% sodium fluoride mouthrinse, and daily use of fluoride toothpaste followed by 0.05% sodium fluoride mouthrinse were more effective than interventions in the control groups (different concentrations or content of fluoride, placebo and no special intervention) in preventing root caries. Fluoride varnish A 2013 Cochrane systematic review of 22 randomized controlled trials (12 455 participants) assessed the effectiveness of fluoride varnishes in preventing dental caries in children and adolescents (14). The primary outcome measures were caries increment measured by the change in decayed, missing and filled tooth surfaces in both permanent and primary teeth. Compared with placebo or no treatment, fluoride varnishes (applied two to four times a year) significantly reduced decayed, missing and filled tooth surfaces in permanent teeth (PF 43%, 95% CI 30% to 57%; 13 randomized controlled trials, moderate quality evidence) and in primary teeth (PF 37%, 95% CI 24% to 51%; 10 randomized controlled trials, moderate quality evidence). No significant associations were found between estimates of effect and baseline caries severity, background exposure to fluorides, application features (such as prior prophylaxis), concentration of fluoride, or frequency of application. A 2020 Cochrane systematic review of 11 randomized controlled trials (3374 participants) evaluated the relative effectiveness of dental sealants compared with fluoride varnishes, or dental sealants plus fluoride varnishes compared with fluoride varnishes alone for prevention of dental caries in occlusal surfaces of permanent teeth in children and adolescents (15). No significant difference was seen between resin-based sealants and fluoride varnish for preventing caries in first permanent molars at 2–3 years of follow-up (odds ratio (OR) 0.67, 95% CI 0.37 to 1.19; four randomized controlled trials, 1683 participants). There was also low certainty evidence that resin-based sealant plus fluoride varnish was superior to fluoride varnish alone (OR 0.30, 95% CI 0.17 to 0.55; one randomized controlled trial, 92 participants). Combination treatment A 2004 Cochrane systematic review of 12 randomized controlled trials (5946 participants) compared the effectiveness of combined topical fluoride therapy versus topical fluoride monotherapy (mainly toothpaste) for the prevention of dental caries in children (16). From the meta-analysis of the effect of fluoride mouthrinses, gels or varnishes used in combination with fluoride toothpaste versus fluoride toothpaste alone, combined treatment significantly reduced decayed, missing and filled tooth surfaces in permanent teeth (PF 10%, 95% CI 2% to 17%; nine randomized controlled trials, 4026 participants). Separate meta-analyses of fluoride gel or mouthrinse combined with toothpaste versus toothpaste alone favoured the combined regimens, but differences were not statistically significant.

Harms

Potential harms of topical fluorides are associated with over-ingestion, leading to symptoms of nausea and vomiting, and dental fluorosis (while tooth enamel is developing, up to 6 years) (17). Use of topical fluoride gel, mouthrinse and varnish preparations is contraindicated in cases of ulcerative gingivitis because of the increased risk of systemic fluoride absorption. Fluoride gel The 2015 Cochrane systematic review of fluoride gels for preventing dental caries in children and adolescents found no reports of adverse effects (11). Ingestion can be prevented by seating the patient upright, not overfilling application trays, use of well-fitted or custom trays, use of a suction device and by separate insertion of upper and lower trays. Gagging may occur in young children during application (18). Studies suggest that professionally applied fluoride gel has a low risk of causing dental fluorosis, even in children younger than 6 years, as it is applied relatively infrequently (19). Fluoride mouthrinse The 2016 Cochrane systematic review of fluoride mouthrinses for preventing dental caries in children and adolescents reported limited information on the possible adverse effects or acceptability of the treatment regimen in the included trials (12). Incompletely reported data on tooth staining were available from three trials, and on mucosal irritation/allergic reaction from one trial. No trials reported on acute adverse events during treatment. The 1994 WHO report on fluorides and oral health raised concern about alcohol-based fluoride mouthrinse formulations. The report noted that such preparations were costly and that there was no justification, other than flavour and formulation, to use an alcohol base. Daily use and inadvertent or intentional ingestion of alcohol-based fluoride mouthrinses should be strongly discouraged. The concern related to a potentially increased risk of oral and

oropharyngeal cancers, where harmful use of alcohol is a key risk factor (20). A 2020 systematic review found no evidence of an increased risk of oral cancer associated with use of alcohol-based mouthrinses alone; however, in the presence of other risk factors, there may be a potentially increased risk that would justify discouraging use. Moreover, no added therapeutic benefit of alcohol-based formulations was identified (21). Fluoride varnish The 2013 Cochrane systematic review of fluoride varnishes for prevention of dental caries in children and adolescents found little information on possible adverse effects or acceptability of treatment (14). When fluoride varnishes are applied professionally and used as recommended, fluoride is not ingested in significant amounts or over an extended period of time, making systemic adverse effects unlikely (17). A study of the pharmacokinetics of fluoride after application of 5% sodium fluoride dental varnish in six children aged between 12 and 15 months found that fluoride exposure levels were lower than the known toxicity level and did not exceed limits for dental fluorosis (22). A prospective study in the United States of more than 10 000 fluoride varnish applications in children aged 0–5 years observed no treatment-related adverse events (23).

Cost / cost effectiveness

Evidence on the cost and cost–effectiveness of fluoride formulations for prevention of dental caries is limited, primarily consisting of studies conducted in school-based programmes. A 2020 scoping literature review aimed to identify evidence on the cost–effectiveness of school-based interventions for caries prevention globally (29). The review included 15 studies, nine published after 2011 and 11 from high-income countries. Almost 80% of the studies assessed the cost–effectiveness of topical fluoride therapies and fissure sealants. The review found evidence to suggest that school-based caries preventive methods were cost-effective and in some cases cost-saving. Evidence from low- and middle-income countries was lacking. A study in Chile compared the cost–effectiveness of seven caries prevention programmes among schoolchildren from a societal perspective, namely water fluoridation, salt fluoridation, dental sealants, milk fluoridation, fluoride mouthrinse, fluoride gel and supervised toothbrushing with fluoride toothpaste (30). Four programmes showed net savings per diseased tooth averted: salt fluoridation (US$ 16.21); water fluoridation (US$ 14.89); milk fluoridation (US$ 14.78); and fluoride mouthrinse (US$ 8.63). The remaining programmes were associated with costs per diseased tooth averted: fluoride gel (US$ 21.30); dental sealants (US$ 11.56); and supervised toothbrushing with fluoride toothpaste (US$ 8.55). A modelling study assessed the lifelong costs of caries with and without fluoride use based on German epidemiological data (31). Effectiveness and costs for seven fluoride regimes were evaluated, including fluoridated salt, weekly home application of fluoride gel, fluoride toothpaste, professional biannual fluoride applications, and various combinations of these. All fluoride regimes resulted in lower lifetime dental restoration costs (fillings, endodontics, crowns and bridges) than the scenario of no fluoride use. A cluster-randomized trial assessed the efficacy and costs of fluoride varnish application for caries prevention in a high-risk population of 513 South African children (32). In addition to supervised toothbrushing with fluoride toothpaste, participants were randomly allocated to receive fluoride varnish application every 3 months or no additional intervention (control) and followed for 24 months. Dental restorations were received or required in 10.2% of teeth in each treatment group. No significant difference was seen between treatment groups for tooth extractions (3.9% versus 4.1% in the fluoride varnish and control groups, respectively). Fluoride varnish was associated with high initial costs, but follow-up costs were comparable in both groups, resulting in fluoride varnish being significantly more expensive than no additional intervention (control). A retrospective study evaluated caries increment and performed a cost analysis of a school-based programme of biannual fluoride applications for adolescents 12 to 15 years in Sweden (33). The programme was introduced in selected public dental clinics in 2003 and extended to all clinics within the region in 2008. Caries data for three groups of participants were compared: two intervention groups (with participants born in 1993 or 1998) who received fluoride varnish and a control group (with participants born in 1993) who did not receive fluoride varnish. The implementation of the school-based fluoride varnish programme was associated with significantly lower caries prevalence and caries increment in 15-year-olds. Over 4 years, the estimated cost per participant was about €44. Cost–effectiveness and estimated net monetary benefits of a programme of one to five visits for fluoride varnish application were evaluated in a study of children aged 9 to 30 months in Thailand (34). From the provider’s perspective, one to three visits for fluoride varnish application decreased decayed, missing and filled primary teeth and saved costs compared with no visit, one visit and two

visits. From the patient's perspective, the estimated net monetary benefits were positive for up to three visits, although no differences were seen in the incremental cost-effectiveness ratios. A cost–effectiveness analysis estimated the average cost–effectiveness ratio of dental sealants versus fluoride varnish in a school-based setting (35). Over a 4-year period, treatment costs for sealants and varnish were US$ 104.25 and US$ 44.96 per child, respectively. The higher cost of sealants was due primarily to differences in labour (30 minutes of a dentist and dental assistant per sealant application compared with 5 minutes from a school health aide per varnish application). The corresponding average cost–effectiveness ratios were US$ 137 and US$ 102 per carious lesion prevented, respectively. Varnish was more cost-effective than sealants, although the difference was not statistically significant.

WHO guidelines

The 1994 WHO report on fluorides and oral health provides a comprehensive review of the role of fluorides in preventing dental caries, and considers various aspects such as history, pharmacology, preventive effects, risks and side-effects (20). The key recommendations from the report remain consistent with current recommendations, highlighting the enduring significance of fluorides as a valuable tool for preventing dental caries. The 2022 WHO briefing note on prevention and treatment of dental caries emphasizes the use of mercury-free products and minimal intervention, aligning with the Minamata Convention on Mercury Elimination. The note highlights fluoride varnish as a recommended approach, suitable for various populations, including those in urban, rural, remote, and vulnerable areas. Fluoride varnish is recognized for its simplicity, effectiveness, wide acceptance, without need for specialist dental training for its application for (24). The 2019 WHO implementation manual on ending childhood dental caries highlights brushing teeth with fluoride-containing toothpaste and application of fluoride varnish as key interventions for preventing and treating early childhood caries (25). The 2011 World Health Assembly resolution on oral health (26) and the 2022 draft global strategy on oral health (27) stress the urgent need to intensify preventive efforts, particularly for dental caries. These documents highlight the limited access to oral health promotion and prevention programmes, including the use of fluorides for caries prevention. Essential prevention methods, such as water fluoridation, community-based initiatives, topical fluoride applications and access to good-quality fluoride toothpaste, are often unavailable or unaffordable for many people. To address this issue, the draft global oral health action plan was prepared and proposes a series of global targets focused on achieving optimal fluoride levels for population oral health. Additionally, the action plan aims to improve the availability and affordability of fluoride medicines for oral health and includes a target that 50% of countries should include dental preparations listed in the WHO Model Lists in their national essential medicines lists by 2030 (28).

Availability

The applications reported that fluoride gel, mouthrinse (higher strength) and varnish are available as prescription products or via medical/dental distributors for professional use, but it highlighted that availability was often limited in public oral health centres. Lower strength fluoride mouthrinse is available as an over-the-counter product. Procurement of supplies for school-based oral health programmes is generally undertaken by the programme organizers (ministries of health and/or education, or other agencies or organizations).

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