

Silver Diamine Fluoride

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

This application form relates to the inclusion of Silver Diamine fluoride ($\text{AgF}(\text{NH}_3)_2$, also known as Silver Diamine Fluoride (SDF), as part of the new subgroup 30.1 on both the EML and the EMLc. A modification to the existing entry for “sodium fluoride” in group 27 is requested. The entry should be moved to a new category “30. Dental medicines” and a subgroup “30.1. Medicines for dental caries”

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 (primary teeth) and 2.3 billion adolescents and adults (permanent teeth).^{7; 16}

SDF is a clear liquid containing high concentrations of fluoride and silver with an amine link. The silver and fluoride work synergistically to prevent dental caries and to arrest them when formed. SDF is commonly used with a fluoride concentration of 38%. It is effective in preventing and arresting dentine caries in primary and permanent teeth with preventive fractions of 60% and 80% (respectively) across the lifespan for the crowns of primary and permanent teeth, as well as the root surfaces of permanent teeth.²⁰ Clinical studies began more than 50 years ago,^{13; 27} and systematic reviews over 10 years ago.¹⁷ A literature search using the search terms: *(Therapy/Broad[filter]) AND (silver diamine fluoride) AND caries AND (prevention OR arrest)* identified 123 publications (26 clinical trials, 16 systematic reviews). The identified publications are from low-, middle-, and high-income countries indicating wide generalizability of results.

Thanks to its ease of application and the virtual absence of side-effects, indications for the use of SDF are broad and include:¹¹

- People with high caries risk
- People with limited access to conventional dental restorative care
- People who are not able to cooperate during dental restorative treatment due to medical, physical or behavioural issues (people with special needs)
- People with caries that is difficult to treat (i.e. caries in partially erupted teeth and root caries).

The contraindications of SDF comprise people with allergy to fluoride or silver; other significant side effects are not reported.

Role of SDF in therapy includes the antibacterial effects of silver and the remineralizing effects of fluoride.²⁹ SDF is bactericidal and inhibits the growth of biofilms of cariogenic bacteria. SDF reduces demineralization of enamel and dentine in the caries process. After application, a highly mineralised surface rich in calcium fluoride and silver phosphate is formed on carious lesions which arrests the carious process. SDF also inhibits collagenases and protects dentine collagen from destruction.

The material costs of the recommended bi-annual applications are about USD\$0.20/year/person. It can be applied in community settings by health workers (dental/non-dental) after receiving limited training. Overall, SDF treatment is non-invasive, affordable, and safe. Although it stains the carious lesions dark as it arrests them, it provides clinicians an option for caries management when high efficacy is required, other restorative dental care not available or when aesthetics is not a primary concern (e.g. when carious teeth are in non-visible molars and pre-molars).

The expected health-related positive impacts of SDF treatment include the reduced impact on quality of life through reduction of pain and infection from caries, reduced absence in school and at work, as well as significant health system cost savings. Since the application of SDF on teeth does not require extensive dental training, it is an alternative to provide access to dental care for caries in rural, remote and otherwise disadvantaged populations through the primary healthcare system.²⁴

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.
<p>Faculty of Dentistry, The University of Hong Kong, Hong Kong, China</p> <p>WHO Collaborating Center Quality Improvement & Evidence-based Dentistry (WHO CC USA-429), College of Dentistry, New York University, New York, USA</p> <p>Department of Dentistry, Radboud University Medical Centre, Nijmegen, The Netherlands.</p>
4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.
<p>International Nonproprietary Name (INN) : Not available</p> <p>Anatomical Therapeutic Chemical (ATC) code of the medicine is A01AA caries prophylactic agents</p>
5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).
<p>Most available formulations typically contain 38% SDF.²⁰ It contains a high concentration of fluoride ions (44,800 ppm). However, one drop only contains 2.24 mg of fluoride, much lower compared to a typical dose of 5% fluoride varnish which contains 11.3 mg fluoride. With biannual application there is no risk of dental fluorosis in children.^{20; 23} No major adverse effects of clinical relevance were reported in any of the clinical trials.^{4; 5}</p> <p>Age-appropriate dose forms and strengths for administration to infants and children are not required – application doses are the same across all age groups. Calculations (see section 10) indicate that the amount of SDF applied to carious teeth is well below any known toxic dose.</p> <p>There is a body of evidence to support the use of SDF in preventing caries from usage and studies for around 50 years. Among many others, the American Dental Association and the American Academy of Paediatric Dentistry recommend and provide guidelines for appropriate use in clinical practice.^{21; 23}</p> <p>Suggested new entry for EML & EMLc: Silver Diamine Fluoride (SDF)</p> <p>38% SDF solution for topical application on tooth surface once or twice per year</p>
6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.
Individual medicine
7. Treatment details (requirements for diagnosis, treatment and monitoring)
<p>Administration: Oral health provider applies 38% SDF on decayed teeth for approximately 1 minute (without removal of carious tissue) once or twice a year. No monitoring system is required after application.</p> <p>Systematic reviews substantiate SDF's efficacy for caries lesion arrest in primary and permanent teeth, and arrest and prevention of new root caries lesions.</p> <p>Safe—clinical trials that have used it in more than 3800 individuals have reported no serious adverse events.⁴</p> <p>Effective—arrests approximately 80% of treated lesions.^{6; 12}</p> <p>Efficient—can be applied in dental clinics or in school- or community-based settings.^{11; 20}</p> <p>Timely—its ease of application can allow its use as soon as dental caries is clinically diagnosed.^{11; 23}</p> <p>Equitable—its application is equally effective and affordable; with the medicament costing less than USD\$ 0.10 per application, it is a treatment alternative for conventional restorative dental care.^{6; 12}</p>
8. Information supporting the public health relevance.
<p>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</p>

of primary teeth.⁷ 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.¹⁵ 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.

Regarding the assessment of current use, in many countries such as UK, USA, Thailand, SDF is licensed as a desensitizing agent. The American Dental Association (ADA) and American Association of Pediatric Dentistry (AAPD) both support off-label use of SDF in the US and there is no liability associated with its use when supported by the provider's best clinical judgement and the existing body of evidence on effectiveness and safety.^{20; 21; 23}

Target population: people across the life span, and patients with special health care needs

Likely impact of treatment on the disease: SDF application can arrest the progression of existing and prevent the incidence of dental caries by approximately 80%. The procedure itself consists of placing a drop of the solution in a dental dappen dish and then applying a small amount on the dried tooth surface with a disposable micro brush or applicator. The procedure is pain-free and arrested carious lesions do not cause further pain and infection.^{20; 23} SDF treatment is therefore a minimally invasive alternative for treatment for dental caries and is also indicated for people unable to tolerate conventional treatment due to their specific condition.^{3; 21} The expected health-related positive impacts of SDF treatment include the reduced impact on quality of life through reduction of pain and infection from caries, reduced absence in school and at work, as well as significant health system cost savings. Since the application of SDF on teeth does not require extensive dental training, it is an alternative to provide access to dental care for caries in rural, remote and otherwise disadvantaged populations through the primary healthcare system.^{24 24-26}

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

A literature search was conducted in the databases Web of Science (WoS) and Pubmed. The search strategy was "TOPIC: (silver diamine fluoride) OR TOPIC: (silver diamine fluoride) OR TOPIC: (silver fluoride) OR TOPIC: (diamine silver fluoride)". A recent umbrella review supported the effectiveness of SDF in arresting coronal caries in the primary dentition and arresting and preventing root caries in older adults for all comparators.²⁰ In addition, another systematic review summarized available systematic reviews about how the SDF intervenes in the caries process of the primary dentition.¹⁸ The review demonstrated that topical application of SDF was effective in arresting dentinal caries in preschool children (12) and the overall percentage of active carious lesions arrested was as high as 81%. Compared with other management options or placebos, the application of SDF is more effective.² With 2-year follow-up, the application of SDF reduced the development of new dentinal carious lesions significantly, compared with placebo, no treatment, or fluoride varnish.¹⁴ Regarding older people, SDF has been found effective in arresting and preventing root caries.^{22; 28} Annual SDF application arrested root caries at 30-month follow-up by 90%.¹⁰

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

No severe harm and adverse health outcomes due to the application of SDF have been reported. SDF application results in a black stain on the arrested dentine caries lesions, which may cause aesthetic concerns.^{4; 5; 8; 14} Tooth pain or gingival irritation, e.g. white lesions on mucosa, gum swelling, and gum bleaching, rarely occurred after the application of SDF and subsided rapidly.^{4; 5} Gingival and mucosa reactions are generally related to insufficient compliance with application protocols, such as incidents of spill-over from the dental cavity.

As pharmacokinetic studies are difficult to conduct in children to test the silver disposition after topical SDF application, a pharmacokinetic (PBPK) model was developed to predict silver disposition in children. The findings show that the topical application of SDF to prevent or arrest dental caries in children results in plasma and tissue silver concentrations lower than toxic concentration.¹

In summary, the available evidence indicates that it is safe to use SDF as a topic agent to prevent or arrest dental caries in both child and adult population.

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

Topical application of SDF is considered a cost-effective method to prevent and manage dental caries. A US study found that SDF treatment as a caries management strategy reduces Medicaid programme dental care expenditures by averting expensive caries treatment options and preventing complex restorative procedures.⁹ A German study found that compared to chlorhexidine varnish and fluoride rinse, SDF application was more cost-effective. SDF was considered the most effective and least costly option in populations with a high risk of caries.¹⁹

To reach a high preventive effect (80% prevented fraction), application twice per year is recommended at a total material cost of about USD\$0.20.^{12; 17} Since application is possible by community health workers or other trained personnel (non-dentists) the additional implementation costs of programmes using SDF are much lower than other dentist-led other forms of fluoride applications.

The retail price of SDF varies across manufacturers and markets. Different brands and retailers options can be ordered online, depending on the country and location. As an example, in the U.S. an 8ml bottle can be bought at USD\$240 (<https://pro.oralscience.com/products/advantage-arrest-1>), a 3ml bottle at USD\$137 (<https://bit.ly/2UYCCFV>), or a 5ml bottle at USD\$46 (<https://amzn.to/3m6790E>)

Inclusion of SDF on the EML will facilitate bulk procurement for public health programmes, increase availability and reduce costs per treatment unit.

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

SDF is approved as class II medical device by US Food and Drug Administration (FDA)²⁰(see: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?id=1404>)

SDF is available in several countries around the world and can be ordered online from global distributors. In some countries national licensing is limited to SDF use for root caries and desensitization.

Argentina: 38% SDF solution, Fluoroplat, NAF Laboratories, Buenos Aires, Argentina; 38% SDF Solution, FAGamin, Bv. of the Poles 6136, Córdoba, Argentina.

Japan: 38% SDF solution, Saforide, Toyo Seiyaku Kasei Co. Ltd., Osaka, Japan.

USA: 38% SDF solution, Advantage Arrest, Elevate Oral Care LLC, West Palm Beach, Florida, USA.

Thailand: 38% SDF solution, Topamine, Pharmadesign Co. Ltd., Samutprakarn, Thailand

India: 38% SDF solution, e-SDF, 5 ml Bottle, Kids-e-dental Llp, Mumbai, India.

Australia: 38% SDF solution, Riva Star, unit doses, SDI.

Brazil: 30% and 12% SDF solution, CarieStop, Biodinâmica, Ibioporã, PR, Brazil

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

SDF is not included in British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia. To be confirmed

14. Comprehensive reference list and in-text citations.

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