Ingestible Fluoride Drug Products

A Scientific Evaluation of Use, Benefits, and Risks in the Pediatric Population

FDA Center for Drug Evaluation and Research

Table of Contents

EXECUTIVE SUMMARY

While orally ingestible prescription drug products containing fluoride have been used since the 1940s, they have never been reviewed and approved by FDA for safety, effectiveness, or quality. Recent research has raised the possibility that the risks of these unapproved products are understated. In May 2025, FDA Commissioner Marty Makary, M.D., M.P.H., initiated a review of the evidence regarding the risks of orally ingestible fluoride prescription drug products in pediatric populations. FDA subsequently held a public meeting to gather scientific input on this topic, as well as collected public comments through a Federal Register Notice. This scientific assessment complements those efforts by providing an analysis of utilization trends, a high-level examination of the benefits and risks of ingestible fluoride drug products, and a recommendation to further restrict use of ingestible fluoride drug products.

Currently, ingestible single-ingredient unapproved prescription sodium fluoride drug products are marketed as oral chewable tablets and oral drops with products dosed in the range of 0.25 mg to 1.0 mg per day. Per current unapproved labeling, these ingestible fluoride drug products were "developed to provide systemic fluoride for use as a supplement in pediatric patients … living in areas where the drinking water fluoride contents does not exceed 0.6 ppm fluoride." In current unapproved labeling, the tablets are recommended for patients three to 16 years of age, and the drops are recommended for patients six months to three years and older. Use of ingestible fluoride drug products in the United States has declined steadily over the past two decades, with an estimated 500,000 prescriptions dispensed in 2024.

In terms of benefits, the use of ingestible fluoride drug products appears to reduce tooth decay in permanent teeth but not primary teeth. An effective method to prevent tooth decay in all children is through good dental hygiene, including the topical application of fluoride via tooth brushing with fluoridated toothpaste. For children who do not receive adequate fluoride through water and other dietary sources, however, it may be beneficial to supplement their dietary intake with ingestible fluoride drug products based on patient-specific factors.

In terms of risks, dental fluorosis is a well-established adverse effect of fluoride exposure documented in the literature and the FDA Adverse Event Reporting System. Moderate to severe dental fluorosis is a discoloration or staining of the teeth that may result when children are exposed to excessive amounts of fluoride. The available evidence linking fluoride ingestion to other emerging safety concerns – neurocognitive, thyroid, gut microbiome, and weight gain effects – is hypothesis-generating and requires further investigation. From a public health standpoint, potential long-term consequences such as IQ score changes are worth additional exploration, particularly in the youngest pediatric populations.

Overall, out of an abundance of caution, it would be prudent to limit use of ingestible fluoride drug products to children aged three years and older who are at high risk of tooth decay. Since the highest risk window for moderate to severe dental fluorosis is age two for permanent incisors and molar teeth, delaying use of ingestible fluoride drug products until at least age three may help balance the prevention of risks without foregoing potential benefits of preventing tooth decay. Further, ingestible fluoride drug products should be limited to children at high risk for tooth decay, such as those who have a history of tooth decay and lack access to fluoridated drinking water. This recommendation aligns with Commissioner Makary's statement that when it comes to children, FDA should err on the side of safety, while allowing parents and clinicians to

engage in shared decision making informed by patient- and community-specific factors such as water sources and overall fluoride exposure, medical history, and dental hygiene habits.

INTRODUCTION

On May 13, 2025, FDA Commissioner Marty Makary, M.D., M.P.H., instructed the Center for Drug Evaluation and Research (CDER) to evaluate the evidence regarding the risks of systemic fluoride exposure from orally ingestible fluoride prescription drug products in pediatric populations, with the goal of better informing parents and the medical community.[1] The agency set a goal date of October 31 for completing a safety review and public comment period, along with taking appropriate action regarding the availability of ingestible fluoride drug products on the market. In response, CDER issued a Federal Register Notice announcing a public meeting entitled "Use of Orally Ingestible Unapproved Prescription Drug Products Containing Fluoride in the Pediatric Population," as well as establishing a docket for public comment on this topic.[2] In collaboration with the Reagan-Udall Foundation for the FDA, the agency held a public meeting on July 23, 2025, to gather scientific and clinical input and facilitate oral public comment.[3] In addition to capturing key themes from the meeting, the Foundation's summary also highlighted key themes from written comments published to the docket.

This scientific assessment complements those efforts by offering benefit/risk considerations regarding the use of ingestible fluoride drug products in children. The assessment begins with a brief history of unapproved prescription drug products containing fluoride and the context in which ingestible fluoride drug products are currently being discussed, including an overview of sources of ingested fluoride. The next section covers FDA's analysis of key data, including an overview of recent utilization trends, a high-level review of potential benefits from ingestible fluoride drug products, and a high-level review of potential risks from ingestible fluoride drug products. It closes with conclusions on our current perspective, as well as a summary of data gaps and future research directions.

History of Unapproved Prescription Drug Products Containing Fluoride

Tooth decay, also known as dental caries or cavities, remains the most prevalent chronic disease in both children and adults, despite being largely preventable. While acute infections may affect more people annually, tooth decay represents a persistent, cumulative condition affecting most Americans over their lifetime. Although tooth decay has significantly decreased for most Americans over the past 50 years, disparities remain among some population groups. Tooth decay incurs significant financial and non-financial costs for individuals, families, and society. These costs include direct expenses for treatment and indirect costs from lost productivity and decreased quality of life.[4,5]

Ingestible fluoride drops and tablets were first marketed in the United States in the 1940s to prevent tooth decay, particularly in children who lived in areas with low or no water fluoridation. Although ingestible fluoride drug products are still prescribed today, none have been reviewed and approved by FDA for safety, effectiveness, or quality. FDA has previously not taken action to remove such unapproved ingestible fluoride drug products from the market. Currently, ingestible single-ingredient unapproved prescription sodium fluoride drug products are marketed as oral chewable tablets and oral drops with products dosed in the range of 0.25 mg

to 1.0 mg per day. **Appendix 1.1** contains additional information on current unapproved product labeling.

Over the years, numerous U.S. medical and dental organizations, including the American Dental Association and American Academy of Pediatric Dentistry,[6,7] have recommended the use of ingestible fluoride drug products for individuals for whom regular topical treatment is difficult to achieve and those for whom topical fluoride only has been considered insufficient to avoid dental decay. Consistent with these recommendations is the view that topical fluoride and ingestible fluoride are complementary but not duplicative, especially for Americans facing barriers to routine dental treatment. Topical fluoride applications deliver high concentrations of fluoride directly to the tooth surface, while ingested fluoride allows for the incorporation of lower levels of fluoride permanently into the structure of the permanent teeth. Thus, potential benefits and risks of topical fluoride would be short-term, and potential benefits and risks of ingested fluoride would be long-term. Since topical fluoride applications are beyond the scope of this scientific assessment, only the evidence on ingestible fluoride drug products is examined in the "Analysis of Data" section.

Sources of Ingested Fluoride

To help gauge the health impact of ingestible fluoride drug products, it is important to understand the background levels of fluoride that Americans typically consume and to quantify these amounts to the extent possible. The greatest source of ingested fluoride is from water fluoridation in areas where communities fluoridate their drinking water. In 2022, 73% of Americans served by community water systems had access to fluoridated water.[8]

Sources other than community water fluoridation also contribute to the total amount of fluoride ingested daily. These include:

- Foods prepared with fluoridated water,
- Processed foods and beverages manufactured in areas with fluoridated water,
- Foods with naturally occurring fluoride (such as tea, seafood, and certain grapes),
- Inadvertent swallowing of fluoride-containing toothpastes, mouth rinses, and professional fluoride applications,
- Certain medications and supplements that contain fluoride, and
- Infant formula prepared with fluoridated water.

In communities with fluoridated water, typical total daily consumption of fluoride in children between the ages of 6 months and 16 years ranges from 0.40 mg to 3.0 mg.[9] Related to that, drinking water in areas with fluoridated water accounts for between 40% and 70% of total fluoride intake in those children. Current unapproved product labeling for ingestible fluoride drug products includes recommended doses that are adjusted for age and level of community water fluoridation, though not by weight. Children taking ingestible fluoride drug products consistent with the unapproved labeling would be expected to consume levels of fluoride that are equal to or lower than children in areas with community water fluoridation.[10, 11, 12, 13, 14] Further, children taking ingestible fluoride drug products consistent with current unapproved labeling would be expected to consume fluoride below the level associated with potential adverse effects of fluoride, including dental fluorosis.

ANALYSIS OF DATA

FDA continuously monitors the safety of drug products sold in the United States, including marketed unapproved prescription drug products. The safety concerns presented in the scientific literature have generally focused on fluoride levels generated from dietary sources, which are greater than those found in ingestible fluoride drug products marketed in the United States. However, given that ingestible fluoride drug products are predominantly used in young children, and in the context of potential emerging safety concerns, a review of the evidence regarding the risks of ingestible fluoride drug products is appropriate. Some studies suggest an association between ingestible fluoride and several health effects, including thyroid hormones, changes to the microbiome, and possibly decreased IQ. These safety findings are not conclusive, but they warrant continued research and discussion. To round out review of the data, this section also highlights recent utilization trends and a high-level overview of potential benefits of ingestible fluoride drug products.

Recent Fluoride Utilization Trends

To assess the scope of use and examine current utilization patterns, FDA/CDER reviewers obtained annual prescription estimates of ingestible fluoride drug products dispensed from U.S. outpatient pharmacies (retail, mail-order/specialty, and long-term care) from 2020 through 2024. Specifically, these utilization analyses focused on ingestible single-ingredient prescription sodium fluoride products. Proprietary databases available to the Agency were used to perform these analyses. Database descriptions and methodology used are provided in **Appendices 1.2 and 1.3**.

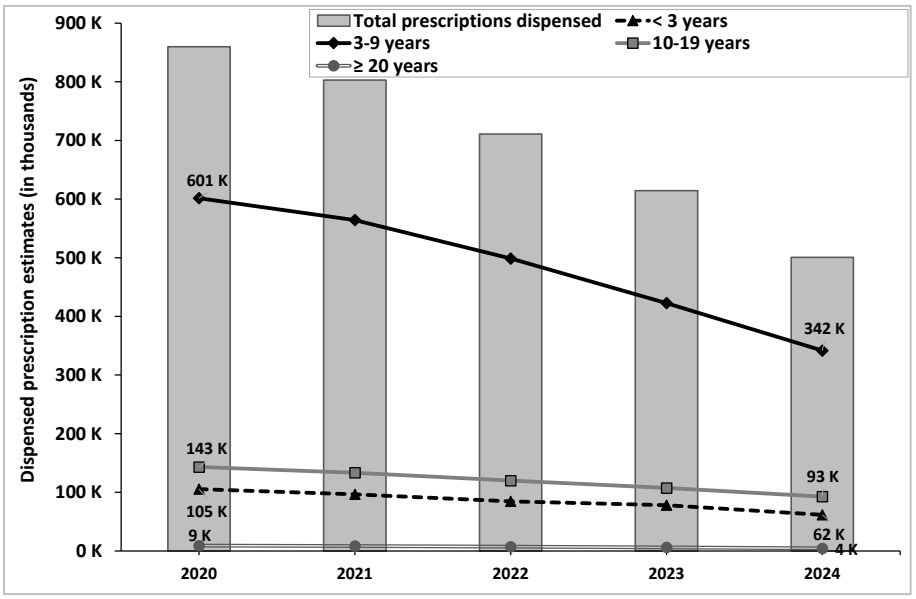
To contextualize the utilization of ingestible fluoride drug products, reviewers also obtained estimates of prescriptions dispensed for ingestible fluoride-containing supplements from U.S. outpatient pharmacies for the most recent year. In 2024, an estimated total of 1.2 million prescriptions were dispensed for ingestible fluoride drug products and fluoride-containing dietary supplements, of which fluoride-containing dietary supplements accounted for approximately 700,000 prescriptions.[15]

Utilization Trends by Patient Age-Groups

Based on dispensed prescription data from U.S. outpatient pharmacies, the use of ingestible fluoride drug products appears to have declined over the past five years, from an estimated 900,000 prescriptions dispensed in 2020 to 500,000 prescriptions dispensed in 2024. This current decreasing trend in use is consistent with historical data, which also showed a steady decline in dispensing from an estimated 2.5 million prescriptions dispensed in 2000.[16]

Figure 1 shows that across the patient age-groups examined, ingestible fluoride drug products were most frequently dispensed to patients aged 3 to 9 years and less frequently dispensed to patients younger than 3 years. Prescriptions dispensed for these age groups accounted for up to 70% and up to 13%, respectively, of the annual total prescriptions dispensed from 2020 through 2024.

Figure 1. Annual Prescription Estimates for Ingestible Fluoride[¥] Drug Products Dispensed From U.S. Outpatient Pharmacies, Stratified by Patient Age-Groups, From 2020 Through 2024



[¥] Includes ingestible single-ingredient sodium fluoride products. Data do not include products administered or provided in other settings of care, such as dental offices, clinics, or hospitals. "K" represents thousands. U.S. outpatient pharmacies include retail, mail-order/specialty, long-term care pharmacies. Data do not include products administered or provided in other settings of care, such as dental offices, clinics, and hospitals.
Source: IQVIA New to Brand. Data years 2020 – 2024. Data extracted May 2025.

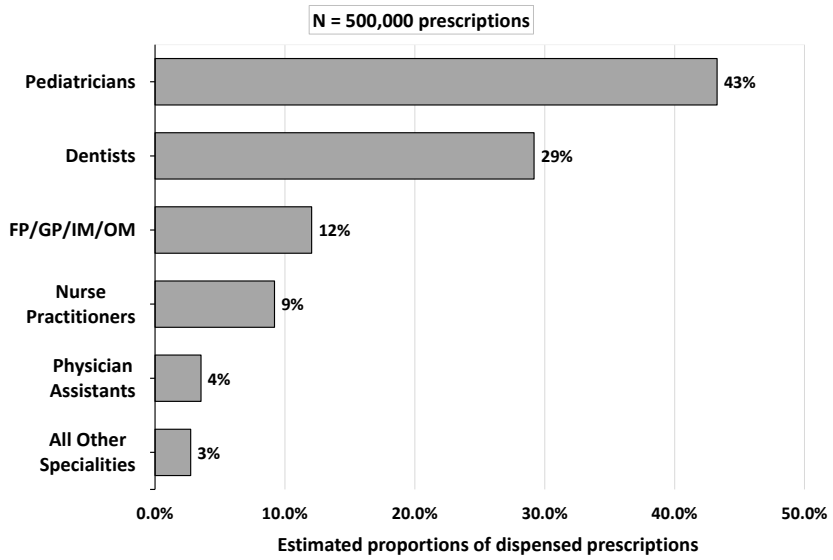
Utilization Trends by Product Formulation and Strength

From 2020 through 2024, the 0.5 mg oral chewable tablets, 1 mg oral chewable tablets, and 0.5 mg/mL oral drops were the most frequently dispensed products from U.S. outpatient pharmacies. In 2024, the 0.5 mg oral chewable tablets accounted for approximately 33%, 1 mg oral chewable tablets accounted for 31%, and 0.5 mg/mL oral drops accounted for 24% of the total prescriptions dispensed.

Utilization by Prescriber Specialty

Figure 2 shows that from 2020 through 2024, pediatricians and dentists were the top prescribers of ingestible fluoride drug products. In 2024, prescriptions written by pediatricians and dentists accounted for approximately 43% and 29% of the total prescriptions dispensed, respectively.

Figure 2. Estimated Proportions of Ingestible Fluoride¥ Prescriptions Dispensed From U.S. Outpatient Pharmacies, Stratified by Prescriber Specialties, 2024



¥ includes ingestible single-ingredient sodium fluoride products. U.S. outpatient pharmacies include retail, mail-order/specialty, and long-term care pharmacies. FP/GP/IM/OM represents family practice, general practice, internal medicine, and osteopathic medicine.
Source: IQVIA National Prescription Audit Extended Insights™. Data year 2024. Data extracted May 2025.

Potential Benefits of Ingestible Fluoride Drug Products

The evidence for a clinical benefit from ingesting fluoride drug products (sometimes called systemic fluoride supplementation) comes primarily from studies conducted from the 1950s through the 1990s, with most research focusing on prevention of tooth decay in children. We examined two systematic reviews focused on the impact of ingestible fluoride drug products on prevention of tooth decay: a 2011 Cochrane review from Tubert-Jeannin and colleagues[17] and a 2008 *Journal of the American Dental Association* (JADA) review from Ismail and Hasson.[18]

Effect on Primary Teeth

Across the two systematic reviews, there were five studies evaluating the efficacy of ingestible fluoride drug products for preventing tooth decay in the primary teeth. Three studies reported benefits to primary teeth, while two studies reported no benefit to primary teeth.

Hu and colleagues (1998) examined the effect of fluoride drops vs. no fluoride drops in Chinese children aged 2 to 3 years, finding a 47% reduction in mean decayed, missing, and filled primary tooth surfaces in the children who used the drops over a three-year period.[19] Mann and colleagues (1989) conducted a retrospective study of Israeli children who received fluoride drops or no fluoride drops, finding that after three years, those receiving fluoride drops had a 43% reduction in decayed, extracted, and filled primary teeth.[20] Lin and Tsai (2000) conducted a three-armed trial, with Taiwanese children aged 2 to 3 years who had cleft lip and/or palate receiving fluoride drops, fluoride tablets, or no treatment for two years.[21] They reported significant reductions in tooth decay, with a 65% reduction in decayed, missing, or filled teeth

(95% CI: 47 to 84%) and a 73% reduction in decayed, missing, or filled surfaces (95% CI: 46 to 99%).

O'Rourke and colleagues (1988) conducted a pragmatic study in which British 5-year-olds were given fluoride tablets or no fluoride tablets over a three-year period.[22] They found no significant effect of fluoride tablets on decayed, missing, or filled primary teeth, reporting a 13% reduction (95% CI: -9 to 35%). Similarly, Petterson and colleagues (1985) reported that there was no statistically significant difference in caries increment in primary teeth between 3-year-old Swedish children receiving (1) fluoride tablets for daily sucking and a fluoride-free toothpaste, (2) a fluoridated toothpaste, (3) fluoride varnish plus a fluoride-free toothpaste, and (4) fluoride varnish plus a fluoridated toothpaste.[23]

These results are challenging to interpret not just because the findings were mixed, but also because the studies occurred in different countries and were rated as being at unclear, moderate, or high risk of bias by the systematic review authors. The Cochrane review rated Lin and Tsai (2000) and O'Rourke and colleagues (1988) as having unclear risks of bias due to missing information, e.g., on selection and attrition bias. The *JADA* review rated the respective risks of bias for Hu and colleagues (1998) as high, Mann and colleagues (1989) as high, and Petterson and colleagues (1985) as moderate. Moreover, both reviews noted that since many of these studies predated the widespread use of topical fluorides, generalizability of these findings to current practice is difficult to predict.

Effect on Permanent Teeth

Across the two systematic reviews, there were reports from five unique studies evaluating the efficacy of ingestible fluoride drug products for preventing tooth decay in the permanent teeth. All five studies reported benefits to permanent teeth.

Based on a pooled analysis of three trials comparing fluoride tablets to no fluoride tablets (Aasenden 1972, DePaola 1968, and Driscoll 1978), Tubert-Jeannin and colleagues reported an overall reduction of 24% in decayed, missing, and filled permanent surfaces (95% CI: 16 to 33%). The first underlying study, Aasenden and colleagues (1972), consisted of three arms, with American children aged 8 to 11 years receiving acidulated phosphate fluoride (APF) tablets diluted in solution, sodium fluoride tablets diluted in solution, or a placebo.[24] The authors found a strong benefit for permanent teeth, reporting a 30% reduction in decayed and filled surfaces for the APF arm and a 27% reduction in decayed and filled surfaces for the sodium fluoride arm compared to placebo. The second study, DePaola and Lax (1968), compared the effect of chewable APF tablets vs. placebo tablets in school-aged American children. They reported a 20% to 23% reduction in tooth decay over two years, as well as a 53% reduction in mean decayed and filled surfaces in permanent teeth erupting during the study.[25] The final underlying publication, Driscoll and colleagues (1978), was part of a broader set of reports on a long-term study on American children initially in the first or second grade, examining them 2.5, 4.7, 6.0, and 7.5 years after starting to receive chewable fluoride tablets.[26,27,28,29,30] Compared to children who did not receive fluoride tablets, the authors consistently found significant reductions in decayed, missing, and filled teeth at each interval. Results ranged from reductions of 6.2% after 2.5 years to 24% after 7.5 years in early-erupting teeth, and 36.5% to 45.9% in late-erupting teeth for the same intervals.

In another study, Allmark and colleagues (1982) examined the effect of fluoride tablets on tooth decay in British school-aged children. After six years, children taking fluoride tablets had a 61% reduction in mean decayed, missing, and filled surface scores compared to children not taking fluoride tablets.[31] A fifth study by Stephen and Campbell (1978) compared the outcomes for British school children who received fluoride tablets for daily sucking for three years to those who received placebo tablets.[32] They reported a 70% reduction in decayed, missing, and filled surfaces in first permanent molars.

All studies found benefits of ingestible fluoride drug products in permanent teeth, and all studies were conducted in American and British pediatric populations. The three studies in the Cochrane review were rated as being at unclear risk of bias due to missing information, e.g., on selection and attrition bias. In the *JADA* review, the risk of bias was rated as moderate for the studies by DePaola and Lax (1968) and Stephen and Campbell (1978), and high for the five reports from Driscoll and colleagues (1974-1981) and the study by Allmark and colleagues (1982). Additionally, as noted earlier, it is challenging to generalize findings from studies that predate the widespread use of topical fluorides.

Summary of Benefits

Based on the studies above, use of ingestible fluoride drug products supports a reduction in tooth decay for the permanent teeth but not the primary teeth. This is consistent with the different mechanisms by which systemic and topical fluoride work: Ingested fluoride acts systemically by becoming permanently incorporated into developing tooth enamel during the window of tooth formation, while topical fluoride is effective only during the times it is in contact with the surfaces of the teeth. For children who do not receive adequate fluoride through water and other dietary sources, it may be beneficial to supplement their dietary intake with ingestible fluoride drug products based on patient-specific factors. More research is needed to confirm these findings in modern populations and with designs and reporting that minimize bias.

Potential Risks of Ingestible Fluoride Drug Products

To better understand the possible health risks of ingestible fluoride drug products in children,[33] FDA reviewers evaluated data from a variety of sources, including the FDA Adverse Event Reporting System (FAERS, described in **Appendix 1.4**) and case reports and epidemiological observational studies in the medical literature (use of artificial intelligence described in **Appendix 1.5**).

Fluorosis

The Centers for Disease Control and Prevention specifically defines dental fluorosis as “a cosmetic condition that affects the teeth” resulting from “overexposure to fluoride during the first eight years of life when teeth are developing under the gums.”[34] Very mild to mild fluorosis, which may be clinically desired as a sign of strong tooth structure with a mild cosmetic impact, typically begins to appear at water fluoride concentrations of 1.5-2.0 mg/L (ppm); this is characterized by faint white lines or spots on teeth. Moderate fluorosis occurs at concentrations of 2.0-4.0 mg/L (ppm); it shows more pronounced white areas and possible light brown staining.

Moderate to severe dental fluorosis has been described as “a condition of the dental hard tissues in which the enamel covering of the teeth fails to crystallize properly, leading to defects that range from barely discernable markings to brown stains and surface pitting.”[35] It is widely recognized as a consequence of excessive systemic fluoride exposure.[36, 37, 38] Severe fluorosis develops at concentrations of 4.0+ mg/L (ppm) and results in brown staining, pitting, and structural damage to tooth enamel. The tooth enamel is hypo-mineralized in severe fluorosis, which can lead to post-eruptive breakdown and loss of the enamel. The adverse effects to dental aesthetics and health due to moderate to severe dental fluorosis indicate the life-long developmental impact of fluoride on the developing tooth. According to Evans and Stamm (1991), the highest risk window for moderate to severe dental fluorosis is at age 2 (22-27 months) for permanent incisors and molar teeth.[39]

The EPA's maximum allowable fluoride level in drinking water is 4.0 mg/L, primarily to prevent severe dental fluorosis, while the secondary standard of 2.0 mg/L is set to prevent moderate fluorosis. The dose, duration, and timing of fluoride intake influence the severity of dental fluorosis.[35] Risk is present between birth up to 8 years of age, but susceptibility is greatest between ages 15-30 months.[35] Current unapproved labeling of ingestible fluoride drug products includes the warning that, “Prolonged daily ingestion of quantities greater than the recommended amount may result in various degrees of dental fluorosis in pediatric patients under age 6 years, especially if the water fluoridation exceeds 0.6 ppm.” Dosing recommendations for ingestible fluoride drug products are therefore based on age and community water fluoride content. See **Appendix 1.1** for relevant current unapproved product labeling information and example dosing tables.

Multiple studies in the published literature evaluated childhood exposure to ingestible fluoride drug products (e.g., tablets, drops) and the development of dental fluorosis in the pediatric population.[36, 37, 38, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56] Most studies indicated a positive association, finding higher dental fluorosis prevalence in ingestible fluoride drug product users compared to non-users, and several reporting statistically significant increases of risk. However, dental fluorosis was generally described as mild.

Consistent with the observational literature summarized above, the FDA Adverse Event Reporting System has also received a few reports (n=5) of dental fluorosis in children following exposure to ingestible fluoride drug products.

Neurocognitive/Decreased IQ

A systematic literature review and meta-analysis of epidemiologic studies by Taylor and colleagues (2025) investigated prenatal or post-natal fluoride exposure and intelligence quotient (IQ) scores.[57] Their literature search yielded 74 studies, most conducted in China, followed by India, Iran, Mexico, and others, and none in the United States. Most studies focused on fluoride exposure through measures of fluoride in drinking water, while some examined fluoride concentrations in urine (measured from maternal or children urine samples, single or multiple collections, which varied by study). Using pre-specified criteria for bias-risk assessment, the majority (n=52) of the studies were considered by the authors to have a high risk-of-bias (low quality). The authors conducted multiple meta-analyses based on the aggregated measurements/estimates from individual studies, if available in the study, and reported an inverse association for various analyses. For example, an association was found between

increased fluoride in urine and decreased IQ scores: For every 1 mg/L increase in urinary fluoride, there was a 1.63 (95% CI: -2.33 to -0.93) IQ point decrease among studies regardless of study quality, and a 1.14 (95% CI: -1.68 to -0.61) IQ point decrease among relatively higher quality studies. There are different scientific opinions regarding the validity and implications of this meta-analysis's conclusions,[58,59] with a number of researchers questioning whether it provides direct evidence to support an association between fluoride and IQ.

Our search of the published literature, which specifically focused on ingestible fluoride drug products in relation to neurocognitive outcomes, identified one study.[60, 61] Broadbent and colleagues (2015) conducted a prospective cohort study in New Zealand using a cohort of 1,037 children born between 1972 and 1973 with several follow-up assessments between ages 5 and most recently, 38 years old (1,007 participants). After adjusting for sex, socioeconomic status in childhood, low birth weight, and breastfeeding (adult IQ also adjusted for educational achievements), compared to never using fluoride tablets, no associations were observed between ever using fluoride tablets and IQ at age 5, ever using in childhood and IQ at age 7 to 13, and ever using in childhood and IQ at age 38.

Thyroid

A systematic literature review of human observational studies assessing the relationship between fluoride and thyroid function or disease was conducted by Iamandii and colleagues (2024).[62] They found that high-fluoride drinking water appears to non-linearly affect thyroid function and increase thyroid stimulating hormone (TSH) release in children. The majority of the studies did not account for iodine intake, which may affect thyroid function. The included cross-sectional study by Du and colleagues (2021) was the only study considered by the authors to have a low risk of bias among the 33 studies evaluated.[63] This was also the only study that adjusted for iodine intake, and they found no association between urinary fluoride and TSH. We did not identify any studies examining ingestible fluoride drug products in relation to thyroid outcomes in the published literature.[60]

Gut Microbiome

Systematic literature reviews by Moran and colleagues (2023)[64] and Yasin and colleagues (2025)[65] yielded four distinct studies in humans that aimed to evaluate the impact of fluoride exposure on the abundance and types of gut microbiota. The implications of this research on the potential association of fluoride exposure are unclear. The studies varied by design (i.e., two ecological studies, one in vitro study,[66] and one cross-sectional study), had exposures from endemic, oral, or injectable fluoride sources, and all used fecal composition as a proxy measure of abundance and types of gut microbiota. All but the injectable fluoride study did not provide measures of fluoride exposure in humans. Further, a study using genetically homogenous sibling pigs suggested that an underestimate of gut diversity was identified through fecal analyses.[67] The authors elaborated that fecal microbiota is an imperfect measure of gut microbiota composition.

We identified one study examining ingestible fluoride drug products (tablets) in relation to the oral microbiome in the published literature.[60, 68] Wolff and colleagues (2019) examined the oral microbiome present in 56 patients recruited from a university dental clinic in Germany between 2008 and 2016. Nineteen samples of carious dentin (severe dentin caries) and 37 supragingival

samples (caries-free controls) were analyzed in relation to oral and periodontal status, socio-demographic parameters, smoking, current use of fluoride products, and childhood fluoride exposure through tablets and salt. The study found a strong correlation between fluoride intake during childhood and specific biofilm species. Current fluoride use did not have a significant effect on the microbiome composition.

Weight Gain

A longitudinal cohort study was conducted in Mexico with enrollment of approximately 500 children at birth between 2007 and 2011 and followed up at ages 4, 6, and 8 years.[69] No associations were observed between dietary fluoride exposures at ages 4 and 6 in relation to body mass index (BMI) z-score at ages 4 and 6, respectively. In cross-sectional analyses of the data, associations were found between higher levels of dietary fluoride intake and higher levels of BMI z-scores at age 8. A cross-sectional study conducted in 2015 in 2,430 children between the ages of 7 and 13 years old in China found a positive association between urinary fluoride concentrations and BMI and obesity.[70] No associations were observed between fluoridated water concentrations and BMI or obesity. Another cross-sectional study used U.S. data in children 6 to 19 years old from the 2015-2016 National Health and Nutrition Examination Survey (NHANES).[71] They found positive associations between urinary fluoride and BMI, urinary fluoride and overweight/obesity, and blood fluoride with weight-adjusted waist index.

We did not identify any studies examining ingestible fluoride drug products in relation to weight gain in the published literature.[60]

Other Risks

Other potential risks of fluoride exposure were mentioned at the July 2025 Reagan-Udall Foundation meeting,[3] with accompanying citations of supportive published studies, and included kidney and liver impairment in adolescents (i.e., lower estimated glomerular filtration rate, higher serum uric acid, and lower blood urea nitrogen),[72] an increase in pediatric bone fractures,[73] lower sex steroid hormones (i.e., total testosterone, estradiol, and sex hormone-binding globulin),[74] sleep disorder symptoms in adolescents,[75,76] and low birth weight in Hispanic newborns (maternal exposure).[77] All of these studies used water fluoride levels to assess fluoride exposure. Additionally, some of the studies also used measurement of either individual plasma or urinary fluoride levels. However, none of the studies mentioned use of ingestible fluoride drug products.

Summary of Risks

Fluorosis is a well-established adverse effect of fluoride exposure. Evidence from literature and FAERS and clear biologic plausibility show that children exposed to excessive amounts of fluoride are at risk of developing dental fluorosis, resulting in discoloration or staining of the teeth, with moderate to severe fluorosis posing a clinical issue. Although a theoretical risk, we found no evidence of skeletal fluorosis associated with oral fluoride ingestion.

The evidence available to support an association between fluoride ingestion and IQ score changes is equivocal in the U.S. population. Epidemiological studies in the published literature were mostly conducted outside the United States, varied by study design and methods, and

reported mixed findings. Interpretation of the data should consider the methods used to assess fluoride exposure and the timing and length of exposure, the tools (and the processes) used to assess intelligence, and the potential bias and confounding from all sources in the study. Meta-analysis of published studies should be interpreted with specific caution because the meta-analysis estimates are quantified from the independent studies, and therefore rely on the quality and accuracy of the independent studies they include. More complexity comes from the lack of confirmed biological connection linking IQ changes to fluoride exposure, the multifactorial trait of IQ, and the unclear clinical significance and practical impact of the small risk estimates. For example, an absolute decrease of 1.14 IQ points per 1 mg/L increase in urinary fluoride might be an overestimate of any decrease in much of the U.S. population, considering that the median baseline fluoride urine level among U.S. youths (<20) has been estimated to be 0.619 mg/L using NHANES data.[78] Moreover, typical prescription doses (0.25 mg, 0.5 mg or 1 mg) of ingestible fluoride drug products would likely result in urine concentrations that fall well below the 1 mg/L standard that the published studies use to measure IQ score decrements in areas with no fluoridation. Similar considerations regarding limitations and interpretation of results apply to studies evaluating a potential association between fluoride exposure and other safety concerns (thyroid, gut microbiome, and weight gain).

CONCLUSIONS

The data described in this scientific assessment support several conclusions. First, use of ingestible fluoride drug products is decreasing over time, with an estimated 500,000 prescriptions dispensed in 2024. Second, potential benefits of ingestible fluoride drug products appear limited to permanent teeth based on the most rigorous analyses of evidence available, which aligns with the mechanism of action for ingestible fluoride. Third, a well-established risk of ingestible fluoride drug products is fluorosis, with moderate to severe fluorosis posing a recognized clinical problem that is documented in the literature and FAERS. Other emerging safety concerns – neurocognitive, thyroid, gut microbiome, and weight gain effects – are more hypothesis-generating and require further investigation. Fourth, there is a pediatric population for which ingestible fluoride drug products may help address unmet medical need. Fifth, additional data are needed to address the gaps in knowledge for both potential short- and long-term benefits and risks of ingestible fluoride drug products.

Given these findings, out of an abundance of caution, our overall recommendation is that the evidence supports limiting use of ingestible fluoride drug products to children aged three years and older who are at high risk of tooth decay. This recommendation aligns clinically with the fact that the highest risk window for moderate to severe dental fluorosis is age two for permanent incisors and molar teeth, so delaying use of ingestible fluoride drug products until at least age three may help balance the prevention of risks without foregoing potential benefits of preventing tooth decay. Additionally, ingestible fluoride drug products should be limited to children at high risk for tooth decay,[79] such as those who have a history of tooth decay and lack access to fluoridated drinking water, as those who are at lower risk for tooth decay would likely gain no additional benefits while being exposed to potential additional risks. This recommendation aligns with Commissioner Makary's statement that when it comes to children, FDA should err on the side of safety.

An important feature of this recommendation is that parents and clinicians would remain able to engage in shared decision making informed by patient- and community-specific factors. Such factors might include water sources and overall fluoride exposure, dietary factors including sugar consumption, family and medical history, and dental hygiene habits. Given the changing landscape of community water fluoridation, some parents and clinicians may find this opportunity to engage in shared decision making regarding ingestible fluoride drug products even more important in the future. Alternatively, they could potentially shift to using fluoride supplements (e.g., vitamins or minerals containing fluoride), as the Centers for Medicare and Medicaid Services are required by law to reimburse for fluoride preparations.[80]

Looking forward, supporting research to address the identified gaps in knowledge about the use, benefits, and risks of fluoride is imperative. For example, limited data exist on how to accurately measure total fluoride exposure from all sources (water, toothpaste, food, beverages, etc.) and how total fluoride exposure relates to both potential benefits and potential risks. The paucity of high-quality research directly comparing ingestible fluoride drug products to other fluoride delivery methods (e.g., water fluoridation and topical applications) greatly limits our understanding. So too does the lack of information available on weight-based dosing, as age-based dosing for ingestible fluoride drug products may be less precise and could lead to fluoride levels that are either too low to provide benefit or too high to avoid risks for certain children. Longitudinal studies designed carefully to avoid bias are needed to examine both the benefits

and risks of ingestible fluoride drug products, especially as many studies in this scientific assessment were conducted prior to widespread access to fluoridated water and therefore may not be widely generalizable today. While this scientific assessment contains recommendations based on current evidence, generating new and better evidence – potentially in partnership with the National Institutes of Health and other Department of Health and Human Services agencies – could inform updated risk/benefit analyses and recommendations.

APPENDICES

1.1 Relevant Product Labeling

Ingestible fluoride drug products are not FDA-approved and therefore do not have approved labeling. Currently (as of 5/28/25) marketed products are summarized in **Table 1**, including indications, dosage form, and relevant product labeling.

Table 1. Relevant Product Labeling Information for Unapproved Prescription Sodium Fluoride Products		
Sodium Fluoride Dosage Form	Chewable tablet[81]	Solution/drops[82]
Labelers of Active Products per EDRLS as of 5/28/2025	Method Pharmaceuticals, LLC Bryant Ranch Prepack Winder Laboratories, LLC	Method Pharmaceuticals, LLC
Strength(s)	0.25, 0.5, or 1 mg	0.5 mg/mL
Indication	For once daily self-applied systemic use as a dental caries preventive in pediatric patients. It has been established that ingestion of fluoridated drinking water (1 ppm F^-) during the period of tooth development results in a significant decrease in the incidence of dental caries. Sodium Fluoride Chewable Tablets were developed to provide systemic fluoride for use as a supplement in pediatric patients from age **3 years to age 16 years and older** living in areas where the drinking water fluoride contents does not exceed 0.6 ppm F.	As a supplemental source of Fluoride. It has been established that ingestion of fluoridated drinking water (1 ppm F) during the period of tooth development results in significant decrease in the incidence of dental caries. Sodium Fluoride Drops were developed to provide systemic Fluoride for use as a supplement in pediatric patients from **6 months to age 3 and older**, living in areas where the drinking water Fluoride level does not exceed 0.6 ppm F.
Overdosage	Prolonged daily ingestion of excessive fluoride will result in varying degrees of fluorosis. Accidental ingestion of large amounts of fluoride may result in acute burning in the mouth and sore tongue. Nausea, vomiting, and diarrhea may occur soon after ingestion (within 30 minutes) and are accompanied by salivation, hematemesis, and epigastric cramping abdominal pain. These symptoms may persist for 24 hours. If less than 5 mg fluoride/kg body weight (i.e., less than 2.3 mg fluoride/lb body weight) have been ingested, give calcium (e.g., milk) orally to relieve gastrointestinal symptoms and observe for a few	Prolonged daily ingestion of excessive Fluoride may result in varying degrees of dental fluorosis. The total amount of Sodium Fluoride in a bottle of 50 mL (0.5 mg/mL) Sodium Fluoride Drops (25 mg F) conforms with the recommendations of the American Dental Association for the maximum to be dispensed at one time for safety purposes. If overdose is suspected, call 1-800-222-1222 (American Association of Poison Control Centers), your local poison control center (www.aapcc.org), or emergency room immediately for treatment recommendations.

Table 1. Relevant Product Labeling Information for Unapproved Prescription Sodium Fluoride Products		
Sodium Fluoride Dosage Form	Chewable tablet[81]	Solution/drops[82]
	hours. If more than 5 mg fluoride/kg body weight (i.e., more than 2.3 mg fluoride/lb body weight) have been ingested, induce vomiting, give orally soluble calcium (e.g., milk, 5% calcium gluconate or calcium lactate solution) and immediately seek medical assistance. For accidental ingestion of more than 15 mg fluoride/kg body weight (i.e., more than 6.9 mg fluoride/lb body weight), induce vomiting and admit immediately to a hospital facility. A treatment dose of Sodium Fluoride Chewable Tablets contains 0.25, 0.5 or 1.0 mg fluoride. The treatment of choice depends upon the age of the child and the water fluoride content. A bottle of 120 0.25 mg tablets contains 30 mg fluoride. A bottle of 120 0.5 mg tablets contains 60 mg fluoride. A bottle of 120 1.0 mg tablets contains 120 mg fluoride. [The total amount of sodium fluoride in a bottle of 120 Fluoride Chewable Tablets (all strengths) conforms with the recommended amount of the American Dental Association for the maximum to be dispensed at one time for safety purposes.]	
Warning	Prolonged daily ingestion of quantities greater than the recommended amount may result in various degrees of dental fluorosis in pediatric patients under age 6 years, especially if the water fluoridation exceeds 0.6 ppm. Read directions carefully before using. **This product, as all chewable tablets, is not recommended for children under age 3 due to risk of choking**. Keep out of the reach of infants and children.	Prolonged daily ingestion of quantities greater than the recommended amount may result in various degrees of dental fluorosis in pediatric patients under age 6 years, especially if the water fluoridation exceeds 0.6 ppm. Read directions carefully before using. Keep out of the reach of infants and children.
Adverse Reactions	Allergic rash and other idiosyncrasies have been rarely reported.	

Table 2 is an example of a dosing table on the label of sodium fluoride chewable tablets.[81]

Table 2. Dosing for Sodium Fluoride Chewable Tablets			
	Water F^- Content		
Ages	**0 ppm F^- to <0.3 ppm F^-**	**0.3 ppm F^- to 0.6ppm F^-**	**>0.6ppm F^-**
3 yrs. to 6 yrs.	0.5mg*	0.25mg*	0
>6yrs. to 16 yrs.	1.0mg*	0.5mg*	0
* Per day			

Table 3 is an example of a dosing table on the label of sodium fluoride solution/drops.[82]

Table 3. Dosing for Sodium Fluoride Chewable Solution/Drops			
AGE	**Fluoride Ion Level in Drinking Water (ppm)***		
	< 0.3 ppm	**0.3 - 0.6 ppm**	**> 0.6 ppm**
Birth to 6 months	None	None	None
6 months to 3 years	Half dropperful 0.25 mg F (1/2 mL)	None	None
3 to 6 years	One dropperful 0.5 mg F (1 mL)†	Half dropperful 0.25 mg F (1/2 mL)	None
6 to 16 years	Two dropperfuls 1 mg F (2 mL)	One dropperful 0.5 mg F (1 mL)	None
* 1.0 ppm = 1 mg/Liter † 1.1 mg Sodium Fluoride contains 0.5 mg Fluoride ion			

1.2 Drug Utilization Methodology

FDA reviewers obtained annual prescription estimates of ingestible fluoride drug products dispensed from U.S. outpatient retail, mail-order/specialty, and long-term care pharmacies, from 2020 through 2024, using the IQVIA New to Brand, Patient Insights, database. The analyses focused on utilization patterns across patient age-groups (<3, 3 – 9, 10 – 19, ≥20 years of age), product formulation and strength, and prescriber specialties. The patient age-groups were defined by the available data categories in the database used.

1.3 Drug Utilization Databases

IQVIA National Prescription Audit New To Brand™

NPA New to Brand (NTB) provides enhanced visibility into the volume of a patient's true, first-time use of a brand. With IQVIA's patented patient deidentification algorithm, this longitudinal data allows users to analyze new therapy starts, switched to/add-on products, and continued therapies within a predetermined look back period (typically 12 months, shorter for acute markets). In addition to reporting the new or refill information from a prescription, the therapy history for the patient is accounted for to categorize that prescription. Data are available through IQVIA's business intelligence tool SMART for 72-rolling months and are updated monthly

IQVIA Smart U.S. Launch

IQVIA Smart U.S. Launch provides a repository on the U.S. marketplace from 1992 to present, capturing both prescription and sales data. Data are available through IQVIA's business intelligence tool SMART and are updated quarterly.

1.4 Description of the FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

1.5 Use of Artificial Intelligence (AI)

FDA reviewers used the internal generative AI solution, ELSA, to assist with filtering abstracts, identifying pertinent articles, and summarizing key findings of articles. FDA reviewers subsequently reviewed and verified all ELSA output, making any necessary revisions.

ENDNOTES

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