Memorandum

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Through

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Subject Updated review of available information pertaining to tianeptine: lack of general recognition of safety for its use in foods.

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Acting Director, OFAS, CFSAN [redacted]

Keywords: Tianeptine; Coaxil; Stablon; Tianeptina; Tianeptinum; Tatinol; Tianeptine Acid; (3-chloro-6-methyl-5,5-dioxo-6,11-dihydrodibenzo(c,f)(1,2)thiazepin-11-yl)-7-aminoheptanoic acid; 7-[(3-chloro-6-methyl-5,5-dioxo-11H-benzo[c][2,1]benzothiazepin-11-yl)amino]heptanoic acid; CAS# 1420-49-1.

This is an addendum to the October 22, 2018 memorandum that discussed the regulatory status and review of available information pertaining to tianeptine use in food. FDA previously concluded that based on the current status of data and information, tianeptine did not meet the experience based on common use in food (prior to 1958) criterion or the technical evidence of safety and the general recognition of safety necessary for it to be GRAS for use in food. Furthermore, the available information suggested that tianeptine use in food may be harmful.

The Division of Food Ingredients' (DFI) toxicology review team was asked to conduct an updated literature review to evaluate if any new scientific information has become available which would amend our previous conclusion regarding the GRAS status of tianeptine use in

food. This addendum summarizes the findings of an updated search of publicly available information since the previous search was completed on October 11, 2018.

Overview of Tianeptine

Tianeptine is a dibenzothiazepine that possesses distinct pharmacologic activity relative to prototypical members of the tricyclic antidepressant chemical class. Tianeptine acts as a serotonin selective reuptake enhancer, not an inhibitor like other tricyclic antidepressants, and acts as a μ-opioid and δ-opioid receptor agonist (Michienzi & Borek, 2022). Tianeptine is an approved drug in several countries in Europe, Asia, and Latin America for treatment of major depressive disorder and anxiety. Tianeptine is not an approved drug in the United States. Tianeptine use can produce clinical effects and dependence symptoms similar to other opioid drugs. The available literature contains numerous case reports that detail serious adverse effects and death associated tianeptine use/withdrawal and suggests an increased potential for tianeptine abuse by the general public. Tianeptine is reported to have the CAS #: 66981-73-5 and is marketed under various trade names: Coaxil, Stablon, Tianna, and ZaZa, among others.

Literature Search Parameters and Results

A search of the scientific literature published since October 11, 2018 through March 16, 2023 was in two databases– PubMed[1] and Web of Science Core Collection[2]. The results from PubMed and Web of Science Core Collection database using the search terms “tianeptine”, “coaxil”, “stablon”, and “tianna”, and a publication date between October 11, 2018 and March 16, 2023 are summarized in Table 1.

Table 1: Summary of literature search terms and results.

Search Terms	Database	Search Results (Number)
Tianeptine	PubMed	68
	Web of Science (Core Collection)	82
Coaxil	PubMed	1
	Web of Science (Core Collection)	3
Stablon	PubMed	2
	Web of Science (Core Collection)	2
Tianna	PubMed	1
	Web of Science (Core Collection)	1

Based on these search criteria, 88 new results related to tianeptine were identified, however,

[1] Pubmed, https://pubmed.ncbi.nlm.nih.gov/, search query publication date between October 11, 2018 and March 16, 2023.
[2] Web of Science, http://www.webofknowledge.com/, search query publication date between October 11, 2018 and March 16, 2023.

none were considered relevant to support the safe use of tianeptine as an ingredient in food. The identified literature consisted of publications describing pharmacologic and potential therapeutic effects of tianeptine for treatment of various disease states/conditions including major depressive and cognitive disorders (Garcia-Alberca et al., 2022; Han et al., 2022). Purported efficacy or benefits of tianeptine are not relevant to the determination of safety and such effects are reminiscent of drugs and not considered supportive of a GRAS conclusion for use in food. Moreover, the recent literature contained numerous clinical case reports detailing severe adverse health effects related to tianeptine intoxication and withdrawal.

No recently conducted oral toxicology studies that are relevant to evaluate the safe use of tianeptine as an ingredient in food were identified in the updated literature query. Several studies utilized laboratory rodent models to investigate tianeptine bioactivity, and effects related to neurofunction and depression, among others (Peric et al., 2020; Peric et al., 2022). A recent study reported opioid-like adverse effects of tianeptine in male rats and mice (Baird et al., 2022). Tianeptine was associated with resistance to tolerance and dependence in a rat model of intracranial self-stimulation (ICSS). ICSS is a behavioral paradigm in which rodents can self-administer rewarding electrical brain stimulation and can be used to assess how pharmacologic treatment affects the function of brain reward systems. Additionally, tianeptine treatment produced opioid-like effects in male mice, including increased locomotor activity, decreased gastrointestinal motility, and depressed respiration. Furthermore, tianeptine effects on ICSS depression in rats and locomotor and respiratory activity in mice was attenuated by administration of opioid receptor antagonists. The design of these studies and assessed parameters were markedly insufficient to establish a safe use of tianeptine as an ingredient in human food or address the reports of serious safety concerns (FDA, 2000).

The generally available literature contained clinical studies investigating the therapeutic efficacy of tianeptine treatment. A 12-month retrospective study by García-Alberca et al. (2022) investigated the antidepressant effects of tianeptine and other anti-depressant therapies in 126 Alzheimer's disease patients (Garcia-Alberca et al., 2022). Tianeptine treatment (25 mg/day) was associated with antidepressant effects and enhanced cognitive performance based on decreased Cornell Scale for Depression in Dementia (CSDD), Hamilton Depression Rating Scale (HDRS), and Neuropsychiatric Inventory subscale D (NPID) total scores and Mini-Mental State Examination (MMSE), Rey Auditory Verbal Learning Test (RAVLT), Category Fluency Test (CFT), Letter Fluency Test (LFT), and Boston Naming Test (BNT) total scores, respectively. The authors also noted that tianeptine was well tolerated during the duration of the study with minimal side effects (nausea, headache, constipation, dizziness) and no changes in the assessed blood and urine clinical parameters (not specified). Notably, the limited duration, design, and assessed parameters of these small-scale clinical studies are insufficient to establish safe levels of tianeptine use in food for the general population. Moreover, these studies do not support determination of a no-observed adverse effect level (NOAEL) or other information relevant to risk assessment or establishing an acceptable daily intake (ADI) level for tianeptine.

Tianeptine is characterized as an emerging substance of abuse and growing threat to public health (Lauhan et al., 2018; Michienzi & Borek, 2022; "NewsCAP: The CDC identifies a potential public health risk from tianeptine," 2018) Several publications described increased frequency of poison control center calls related to tianeptine exposure, and clinical case reports of tianeptine intoxication and withdrawal. Marraffa et al. (2018) highlights the potential for

tianeptine abuse, dependence, and withdrawal based on a retrospective study of calls to the New York State Poison Control Centers between January 1, 2000 and April 1, 2017 (Marraffa et al., 2018). The authors identified nine reported cases related to tianeptine, five of which described presentation of symptoms consistent with opioid withdrawal. Additionally, one report of tianeptine abuse was associated with onset of respiratory depression, which was reversed following administration of naloxone, an approved drug commonly administered to reverse effects related to opioid overdose. The Alabama State Poison Center identified 48 cases related to acute tianeptine intoxication and withdrawal between January 1, 2015 and March 15, 2020 (Rushton et al., 2021).The authors noted that half of identified tianeptine cases required medical admission and a third of cases required treatment in the intensive care unit.

Karim and Ioannou (2020) described a case report in which a 28-year-old woman with a history of schizoaffective disorder bipolar type and poly-substance use was involuntarily admitted to an acute inpatient psychiatric facility due to symptoms of aggression and psychosis related to tianeptine abuse (Karim & Ioannou, 2020). Patient testimony acknowledged elevated use of tianeptine (~100 mg/day) to alleviate symptoms of depression and anxiety. Family members attested that the episodes of physical and verbal aggression coincided with tianeptine use. The authors noted that the patient's symptoms subsided upon cessation of tianeptine use and there was no evidence of other etiologies based on serum and urine laboratory results. A meeting abstract by Abdu et al. (2019) summarized the findings of a case report in which a 23-year-old male presented with multiple new onset seizures following tianeptine intake (Abdu et al., 2019). The patient experienced auditory and visual hallucinations and required intubation and medical intervention to address muscle rigidity and acute renal injury. Notably, urine drug screening was negative for drugs of abuse, and following recovery, the patient reported experiencing similar symptomology following tianeptine withdrawal. Additionally, several publications and abstracts discuss naloxone and buprenorphine treatment to address withdrawal symptoms following cessation of tianeptine use (Edgar et al., 2020; Szczesniak & Sullivan, 2022; Trowbridge & Walley, 2019).

A query of the CFSAN Adverse Event Reporting System (CAERS)[3] identified 13 adverse event reports using the search term "tianeptine" and a date range of October 11, 2018 to February 9, 2023. The reports highlight serious safety concerns related to use of products containing tianeptine as an ingredient, including purported incidences of addiction, withdrawal, hospitalization, and death. Cases described in medical journals, in calls to U.S. poison control centers, and in reports to the FDA suggest that tianeptine has a potential for abuse. Furthermore, it suggests that individuals with a history of opioid use disorder or dependence may be at particular risk of abusing tianeptine. The increasing incidence of tianeptine abuse has prompted several U.S. states (Michigan, Alabama, Tennessee, Ohio) to ban the sale and use of tianeptine and/or classify tianeptine as a schedule I/II controlled substance. FDA notes classification of tianeptine as a Schedule I/II controlled substance is cause for serious safety concerns and is contradictory with general recognition of safety of use as a food ingredient.

[3] CAERS is a database of information on adverse event and product complaint reports voluntarily submitted to FDA by consumers or health professionals. Adverse event reports for a given product in CAERS reflect only original information reported to the FDA and do not represent any conclusion by FDA about whether the product was causal to the adverse events. https://www.fda.gov/food/compliance-enforcement-food/cfsan-adverse-event-reporting-system-caers

Overall, no new studies relevant to support the safe use of tianeptine as an ingredient in food were identified in the updated literature review.

Conclusion

Based on the updated literature search, no new information was identified that would amend our conclusion that there is no basis to conclude the use of tianeptine in food is GRAS. FDA reiterates that such reports of serious adverse events associated with tianeptine use are cause for serious safety concerns and are inconsistent with general recognition of safety of use as a food ingredient.

The tianeptine memorandum dated October 22, 2018, contains excerpts which describes the lack of general recognition of safety for the use of tianeptine in "conventional foods." DFI notes and further expands that the available data are insufficient to support the safety of tianeptine for use in "foods generally."

Additionally, tianeptine may be marketed as specific ionic salts which incorporate different counterions. Tianeptine salts are anticipated to disassociate into its tianeptine (active) and counterion components when consumed. Therefore, in the absence of sufficient scientific evidence to demonstrate otherwise, all safety concerns identified in our reviews related to use or presence of tianeptine in foods are pertinent to all salt forms of tianeptine. Accordingly, our previous conclusion regarding the GRAS status of tianeptine use in food dated October 22, 2018, is applicable to all salt forms of tianeptine.

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