U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: , Ph.D.
Special Assistant
Office of Dietary Supplement Programs
Center for Food Safety and Applied Nutrition (CFSAN)

From: , Ph.D., HFS-255
Division Director
Division of Biotechnology and GRAS Notice Review (DBGNR)
Office of Food Additive Safety (OFAS)/CFSAN

Through: , Ph.D.
Toxicology Supervisor, HFS-255

, Ph.D.
Director, OFAS, HFS-200

Date: October 22, 2018

Subject: Regulatory status and review of available information pertaining to Tianeptine: lack of general recognition of safety for its use in conventional foods.

GRAS Provision in Defining a Food Additive

As defined in section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. § 321(s)], the term "food additive" refers to any substance the intended use of which results in its becoming a component of any food, unless the substance is the subject of a prior sanction or is generally recognized as safe (GRAS) among qualified experts under the conditions of its intended use. Furthermore, under section 201(s) of the FD&C Act, a substance is exempt from the definition of a food additive and thus, from premarket approval requirements, if its safety is generally recognized by qualified experts.

As there is no food additive regulation establishing safe conditions of use for Tianeptine as an ingredient in foods, this memorandum will consider the applicability of the GRAS criteria for the use of Tianeptine as an ingredient in foods.

GRAS Criteria

A conclusion that a particular use of a substance is GRAS under the conditions of its intended use requires both general recognition and evidence of safety.

General recognition of safety requires common knowledge, throughout the expert scientific community knowledgeable about the safety of substances added to food, that there is reasonable certainty that the substance is not harmful under the conditions of its intended use. General recognition of safety through scientific procedures must be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods. The usual mechanism to establish that scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal. Mechanisms to establish the basis for concluding that there is common knowledge throughout the expert scientific community about the safety of a substance are more varied. Most often, publication in a peer-reviewed scientific journal of data on a test substance has been used to establish common knowledge throughout the expert scientific community in addition to general availability. These criteria are discussed in the GRAS final rule, which took effect on October 17, 2016 (81 Federal Register (FR) 54960; August 17, 2016).

A demonstration of safety under GRAS criteria requires that information establishing that the intended use of the substance is safe. FDA has defined “safe” (21 CFR 170.3(i)) as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use. FDA's regulations in 21 CFR Part 170 describe the eligibility criteria for classification of a substance added to food as GRAS. Under 21 CFR 170.30(a)-(c), general recognition of safety must be based on the views of qualified food safety experts. The basis of such views may be either through: (1) scientific procedures; or, (2) in the case of a substance used in food prior to January 1, 1958, experience based on common use in food.

FDA's regulations in 21 CFR Part 170 define "common use in food" and establish eligibility criteria for classification as GRAS through experience based on common use in food. Under 21 CFR 170.3(f), common use in food means "a substantial history of consumption of a substance for food use by a significant number of consumers."

Similarly, FDA's regulations in 21 CFR Part 170 define "scientific procedures" and establish eligibility criteria for classification as GRAS through scientific procedures. Under 21 CFR 170.3(h), scientific procedures “include the application of scientific data (including, as appropriate, data from human, animal, analytical, or other scientific studies), information, and methods, whether published or unpublished, as well as the application of scientific principles, appropriate to establish the safety of a substance under the conditions of its intended use." Under 21 CFR 170.30(b), general recognition of safety based upon scientific procedures "shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food

additive." Section 170.30(b) further states that general recognition of safety through scientific procedures is ordinarily based upon published studies, which may be corroborated by unpublished scientific data, information, or methods.

Findings and Conclusions

FDA has searched the relevant scientific databases for information and published literature on Tianeptine and the findings are summarized in Attachment 1. A review of the current literature, focusing on hazard assessment and safety evaluation of Tianeptine, revealed that there are not sufficient data for evaluating its safety for use as a food ingredient. It should be emphasized that because a substance added to food may be consumed by the entire population over a lifetime, assurance of safety requires an evaluation of potential effects of long-term use within the various segments of the population, if appropriate.

Because there is a lack of data in the scientific literature to support the safe use of Tianeptine in food, DBGNR is unable to conclude that the addition of Tianeptine to food meets the statutory criteria for GRAS. Indeed, the available data reveal numerous harmful effects and multiple adverse event reports where the systems that are most commonly affected are the nervous, cardiovascular, and gastrointestinal systems. Therefore, the ingredient cannot be said to meet either the technical evidence of safety or the general recognition of safety necessary for Tianeptine to be GRAS for use in food.

Attachment

Office of Food Additive Safety DBGNR Evaluation of Tianeptine

Overview of Information Available on Regulatory Status and Review of GRAS and Safety Considerations

Evaluation of food ingredient (vs. food additive) status of compound and assessment of its possible GRAS classification[1]

Names Used for Compound[2]: 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
PubChem CID for Compound: 68870 (Molecular Formula: $C_{21}H_{25}ClN_2O_4S$)
CASRN for Compound: 1420-49-1
Searches Performed: Compound names noted above were searched alone and/or in combination with other relevant terms (e.g., food ingredient, dietary supplement, safety, toxicity)

Food Ingredient/Substance vs. Food Additive Regulatory Status Determination

Associated Searches:

- Search of "Mintel" (http://portal.mintel.com), a food and consumer products database that includes a search function for food ingredients and is available via the FDA Electronic Library
- Google search for the chemical compound as a "food additive," "food ingredient" or use in conventional food
- Search of the list of Flavor & Extract Manufacturers Association (FEMA) GRAS substances (www.femaflavor.org)
- Search of the US Code of the Federal Register (CFR) for food additive or GRAS status (www.ecfr.gov)
- Search FDA.gov website for food ingredient information which included "GRAS Notices," "Select Committee on GRAS Substances (SCOGS)," and "Substances Added to Food" (formerly "Everything Added to Food in the US (EAFUS)") databases
- Search in FDA.gov website under "FDA.gov archive" webpage (linked to archive-it.org/collection)

Findings:

- No evidence compound has been used in conventional foods in the United States (US) at this time or prior to 1958
- No evidence compound has been evaluated as or considered a GRAS substance by FDA or approved as a food additive
- Does not meet the "common use in food" criterion

Dietary Supplement Availability, Market or Use Status

Associated Searches:

- Google search for dietary supplement products
- Search of FDA.gov website and "FDA.gov archive" webpage (linked to archive-it.org/collection) for dietary supplement products
- Search of "Mintel" (http://portal.mintel.com), a commercial food and consumer products database that includes a search function for "vitamins and dietary supplements," which is available via the FDA Electronic Library
- Search of World Anti-Doping Agency (WADA) website at www.wada-ama.org
- Search of US Anti-Doping Agency website at www.usada.org
- Search National Institutes of Health (NIH) National Library of Medicine (NLM) Dietary Supplement Label Database (DSLD) at www.dsld.nlm.nih.gov

[1] The principal focus of this Division of Biotechnology and GRAS Notice Review (DBGRN)/OFAS evaluation was on determining the status of these compounds in question with respect to being food additives or food ingredient/substances and assessing the GRAS classification of the latter. The examination of the status of these compounds with respect to being dietary supplements or drugs was only done within the context of the "food" determination. It is assumed that the parties responsible for these other products (i.e., dietary supplements by ODSP/CFSAN; drugs by CDER/FDA) will perform evaluations to assess their safe and legal use.

[2] These names represent some but not all names found for this compound. It attempts to reflect some of the more commonly used, found or referenced compound names.

- Search NIH Office of Dietary Supplements – United States Department of Agriculture (USDA) Dietary Supplement Ingredient Database at www.dietarysupplementdatabase.usda.nih.gov

Findings:

- None of the established governmental or commercial databases listed above that survey for dietary supplement products on the US market indicated that dietary supplements containing tianeptine were found in the US
- An internet search for tianeptine revealed that products described as dietary supplements containing this compound are readily available for online purchase in the US. The companies offering these products were identified on their websites as being from the US and from outside the US
- Online resources and forums that provide information on the use of dietary supplements to interested consumers indicate the option of using tianeptine for pain and its nootropic[3] properties[4]
- US FDA Import Alert (#54-16) published 8/2/18 on the FDA.gov website addressed "imported products marketed as dietary supplements that…contain undeclared active pharmaceutical ingredients (APIs)." Under the listing for import alerts (IA) for firms from China were 2 notations for products imported from Suzhou MyLand Pharm & Nutrition Inc. (Jiangsu, China) for which "FDA analysis detected Tianeptine in product." The products were described as "Propolis[5] Extract Powder" and were noted in the IA in one case as "Herbals & Botanicals (no Teas), N.E.C." and in another case as "Anti-Depressant N.E.C."[6]
- Several media and health news sources have reported in the last year or so on the issues associated with individuals consuming dietary supplements that contain tianeptine. In one article, a mother discusses her son's use of a tianeptine dietary supplement for its nootropic properties and its harmful effects on his behavior, health and life. She describes her son's increases in consumed dosages, addiction, severe withdrawal symptoms that required emergency medical treatment, and gradual process of recovery.[7] Other media reports and articles covered the findings of recently published clinical papers that described a case report of the adverse effects experienced by an individual using a tianeptine dietary supplement, and a survey of US poison control center calls associated with the use of tianeptine dietary supplements[8]

Drug Status Determination

Associated Searches:

- Search of "Drugs@FDA" site for "FDA Approved Drug Products" available via the FDA Electronic Library
- Search of "AHFS Drug Information" site, "Orange Book[9]" site, "USP Dictionary Online" site and "Pharmapendium" site available via the FDA Electronic Library
- Search IBM "Micromedex[10]" site available via the FDA Electronic Library
- Search of www.ClinicalTrials.gov at US National Institutes of Health (NIH)
- Search FDA.gov website and FDA archive website (FDA.gov: archive-it.org/collection) for drug information
- Search of following sources from other countries available via the FDA Electronic Library: "British Pharmacopoeia," "European Pharmacopoeia," and "Japanese Pharmacopoeia"

[3] Nootropics are considered compounds that have cognitive enhancing properties in humans

[4] Some examples are at https://liftmode.com/blog/five-supplements-for-pain/ and www.suppwiththat.com/tianeptine/

[5] Propolis is a red or brown resinous substance collected by honeybees from tree buds and is used by them to fill crevices and to seal and varnish honeycombs.

[6] N.E.C. refers to the term "not elsewhere classified."

[7] "The Hidden Dangers of Nootropics" by M. Doyle in "the fix" is found at https://www.thefix.com/hidden-dangers-nootropics

[8] Examples of reference to and discussion of tianeptine as a dietary supplement are at https://gizmodo.com/people-are-getting-sick-from-an-opioid-like-dietary-sup-1828094277, https://www.empr.com/news/unscheduled-psychoactive-pharma-agent-online-purchase-tianeptine/article/681700/, http://www.rightinginjustice.com/news/2017/08/21/man-became-dependent-on-supplement/.

[9] The "Orange Book" represents an electronic version of the "Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations." It identifies drug products approved based on safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (the Act) and search results were for the categories of proprietary name, active ingredient or application numbers.

[10] This resource contains databases covering pharmacology, therapeutics, toxicology and diagnostics.

Findings:

- Tianeptine is not an US FDA approved drug, and thus, is not approved for marketing in the US
- Tianeptine is not approved for use in Canada, United Kingdom, Australia, New Zealand and Japan, among other countries
- Tianeptine is an approved drug for use and marketing in over 60 countries around the world and includes some countries in Europe (e.g., France, Portugal, Bulgaria, Romania, Slovakia, Poland, Malta, Hungary, Lithuania, Czech Republic, Austria, Latvia, and Estonia), Asia (e.g., Singapore, South Korea), Middle East (e.g., Bahrain, Egypt) and South America (e.g., Brazil, Chile, Argentina)
- To address the access of tianeptine via the internet, Australia (March, 2017) and New Zealand (March, 2018) recently classified tianeptine a Schedule 4 substance, meaning tianeptine has restrictive controls on its availability
- Country of Georgia Health Authority withdrew tianeptine from market in June 2010 because of its abuse potential
- Health authorities of Russia (2010), Armenia (2010), Ukraine (2011) and Turkey (2012) placed tianeptine on their respective controlled substance list. Concerns included cases of tianeptine misuse by intravenous injection of drug
- In April 2018, Michigan instituted a statewide ban on the antidepressant tianeptine sodium by classifying the drug in the highly restrictive Schedule II controlled substance category. This action makes Michigan the first state to forbid all legal manufacture, distribution and possession of tianeptine sodium. The state legislature indicated that this ban was driven by the fact that "a spate of gruesome overdoses related to tianeptine sodium scoured the Midland and Saginaw area [of Michigan] in 2017"[11]

(b) (4)

- Three clinical trials evaluating the nature of the effects of tianeptine are listed at the NIH Clinical Trials website. The studies assessed the pharmacokinetics of tianeptine in healthy individuals, or the efficacy of the agent in the treatment of the cognitive impairment associated with major depressive disorder, or of sub-threshold symptoms, continuing psychosocial morbidity and cognitive impairment associated with bipolar depression. They were conducted in Belgium, South Korea and Brazil, respectively
- An internet search for tianeptine indicated that this substance is available for online purchase in the US as a drug product in the form of a tablet, capsule or powder. Some examples of terms used to describe the action of the products include depression, anxiety, mood brightening, nootropic effects, obsessive compulsive disorder and eating disorders. In some instances, the websites also contrastively state that their product is for research purposes only, not intended for human consumption, not intended to diagnose, treat, cure or prevent any disease, and/or not evaluated by the FDA. In addition, some of the companies' website links that are listed in response to an internet search for tianeptine as a drug appear to avoid the actual noting of the term "drug" for the product on their webpages
- Tianeptine in the form of bulk powder material is available for purchase from internet websites from a range of companies in China. In the descriptions of product details, the most common notation for "usage" is the term "animal pharmaceuticals," while often listed under "application" are the terms "anti-depressant or -depression" and "pharmaceutical raw intermediate"
- Several online discussion forums are available that address the purchase and use of tianeptine along with advice on the nature of its effects on consumers and their health conditions and/or mental state

[11] Sources of information on this topic include www.usnews.com/news/best-states/michigan/articles/2018-03-21/snyder-to-receive-bill-on-statewide-tianeptine-sodium-ban and www.freep.com/story/news/politics/2018/04/06/michigan-ban-antidepressant-tianeptine-sodium/494469002/.

(b) (4)

- Online resources that provide information to interested consumers on the use of drugs for self-prescribed treatment purposes are available for tianeptine. These sources[13] provide guidance on the self-medicated use of tianeptine for conditions such as major depressive disorder, anxiety, stress, memory and learning, inflammation, pain, irritable bowel syndrome, asthma
- Numerous media and health news sources have reported in the last year on the nature of and issues with individuals taking the unapproved drug tianeptine in the US. The articles covered the findings of recently published clinical papers that described a case study of an individual that purchased online and used the unapproved drug tianeptine, and a survey of US poison control center calls associated with the use of this antidepressant drug to self-mediate or for recreational purposes. The recent increase in calls were principally from healthcare providers concerned about misuse and abuse of tianeptine along with negative side effects and withdrawal symptoms associated with the drug. Also noted are two recent overdose deaths in the US tied to the online purchase and use of tianeptine[14]

Safety/Toxicity Status and Review

Associated Searches:

- Search of PubMed @ FDA for various names of the compound alone and in combination with terms "safety" or "toxic*" or "adverse"
  -identified ~35 to 550 journal articles on this compound, its metabolism, properties, action and/or health effects or use in disease treatment in separate searches depending on search terms used
- Search of Google Scholar for various names of the compound alone and in combination with terms "safety" or "toxic*" or "adverse"
  -identified from 2,910 to 10,900 reference items depending on search terms used (primarily various published journal or review articles in first 10 pages of search results)
- Search Web of Science via FDA Library for various compound names
  -identified 10 to 625 journal articles on this compound, its metabolism, properties, action and/or health effects or use in disease treatment in separate searches depending on search terms used
- Several references also identified in reference sections of related published journal articles

The scientific and clinical literature on various topics concerning tianeptine is very extensive. Hence, the review of this literature presented below is a representative, and not exhaustive, one. Key points relevant to the hazard assessment and safety evaluation of tianeptine were identified and are stated below in italics after "arrow" bullets. In support of these key points, some representative references are listed in addition to a brief summary on the noted key point.

Findings:

➢ *Tianeptine acts at several sites and systems in the central nervous system (CNS) to produce its characteristic effects in humans*

- Gassaway MM, Rives M-L, Kruegel AC, Javitch JA, Sames D. The atypical antidepressant and neurorestorative agent tianeptine is a μ-opioid receptor agonist. Transl Psychiatry 4: e411-416, 2014

- McEwen BS, Chattarji S, Diamond DM, Jay TM, Reagan LP, Svenningsson P, Fuchs E. The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. Mol Psychiatry 15(3): 237-249, 2010

[13] Examples are www.selfhacked.com/blog/tianeptine/ and www.tianeptinestore.com/tianeptine-sulphate-dosage-complete-guide-2016/.

[14] Examples of reference to and discussion of tianeptine as a drug are at www.ajc.com/news/health-med-fit-science/what-tianeptine-cdc-warns-unapproved-opioid-like-antidepressant-poisoning-people/rXOlp3ZNbiLP7tScdOH3EO/, www.cnn.com/2018/08/03/health/tianeptine-antidepressant-poison-control-cdc-study/index.html, www.newsweek.com/what-tianeptine-cdc-issues-warning-dangerous-drug-becoming-more-popular-1055149, www.webmd.com/mental-health/addiction/news/20180802/opioid-addicts-turning-to-unapproved-antidepressant and www.healthline.com/health-news/controversy-over-antidepressant-tianeptine.

- Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, Bartolomucci A, Fuchs E. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. PNAS 98(22): 12796 – 12801, 2001

  Tianeptine acts via complex and distinctive mechanisms which involve several sites and systems in the CNS. It acts on neuronal receptors for monoamine neurotransmitters in the brain. This includes producing changes in extracellular serotonin levels, and increasing dopamine signaling in the mesocortical-limbic dopamine pathway (or reward pathway) along with dopamine levels in the cerebral cortex and other brain regions. Tianeptine also modulates glutamate receptor activity in the amygdala and hippocampus of the brain. The key function of glutamate involvement in tianeptine action is to affect the release of brain-derived neurotropic factor (BDNF) which, in turn, alters central neuroplasticity and neuromodeling in addition to cellular density and cellular resistance to stressors. Tianeptine is also thought to affect the neural networks between the hippocampus and prefrontal cortex in a similar fashion. Some recent evidence suggested that "tianeptine's modulation of the glutamatergic system may occur indirectly, via activation of opioid receptor signaling." Tianeptine has been shown to act as an agonist at μ- and δ-opioid receptors.

➢ *Tianeptine was developed and is used as a drug to treat diagnosed diseases and medical conditions*

- Defrance R, Marey C, Kamoun A. Antidepressant and anxiolytic activities of tianeptine: An overview of clinical trials. Clin Neuropharmacol 11 (Suppl 2): S74 - 82, 1988

- Wilde MI, Benfield P. Tianeptine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. Drugs 49(3): 411-439, 1995

- Wagstaff AJ, Ormrod D, Spencer CM. Tianeptine: A Review of its Use in Depressive Disorders. CNS Drugs 15 (3): 231-259, 2001

- Yoo I, Woo J-M, Lee S-H, Fava M, Mischoulon D, Papkostas GI, Kim E-J, Chung S, Ha JH, Jeon HJ. Influence of anxiety symptoms on improvement of neurocognitive functions in patients with major depressive disorder: A 12-week, multicenter, randomized trial of tianeptine versus escitalopram, the CAMPION study. J Affective Disorders 185: 24-30, 2015

- DrugBank, an online bioinformatics and chemoinformatics resource for information on drugs. Tianeptine, Accession number DB09289, DrugBank version 5.1.1, released 7/3/2018

  Tianeptine was principally developed as a drug to treat depression and concomitant anxiety. It has been investigated for its effects on several forms of depression such as major depressive disorder, bipolar depression, dysthymia (or persistent mild depression), and stress response syndrome (or situational depression) in addition to depression associated with alcohol dependence and/or withdrawal. Clinical trial research has also examined the efficacy of tianeptine in addressing the cognitive impairment and psychosocial morbidity associated with depression. Tianeptine also has been studied for its use in the treatment of other medical conditions such as irritable bowel syndrome, asthma, fibromyalgia, posttraumatic stress disorder, and preliminarily, attention-deficit hyperactivity disorder. Tianeptine has been approved in numerous countries for use as a drug for its pharmacological effects in the treatment of certain diseases or disorders.

➢ *Tianeptine has atypical pharmacological and unique functional properties for a tricyclic antidepressant compound*

- Gassaway MM, Rives M-L, Kruegel AC, Javitch JA, Sames D. The atypical antidepressant and neurorestorative agent tianeptine is a μ-opioid receptor agonist. Transl Psychiatry 4: e411-416, 2014

- McEwen BS, Chattarji S, Diamond DM, Jay TM, Reagan LP, Svenningsson P, Fuchs E. The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. Mol Psychiatry 15(3): 237-249, 2010

- PubChem, Open Chemistry Database. Tianeptine, Compound Summary for CID 68870. US National Library of Medicine, National Center for Biotechnology Information. Downloaded on 8/28/2018

  Tianeptine is classified as a tricyclic antidepressant because of its heterocyclic ring structure making it structurally similar to other tricyclic antidepressants (TCA). However, the neurochemical profile and pharmacological properties of tianeptine are different from other typical TCAs. Traditional TCAs are recognized principally to inhibit reuptake of norepinephrine and serotonin (i.e., SNRIs or serotonin-norepinephrine reuptake inhibitors) into axon terminals which serves to increase the level of these two neurotransmitters in the brain. In contrast, tianeptine affects brain serotonin differently as it is a serotonin selective reuptake enhancer (SSRE), not inhibitor like other TCAs. In addition, unlike traditional TCAs, tianeptine also affects the dopamine and glutamate brain neurotransmitter systems. Tianeptine also acts as a neuromodulator by being an atypical but full μ-opioid and δ-opioid[15] receptor agonist and by releasing brain-derived neurotropic factor (BDNF). The fact that naloxone, an opiate blocker, has successfully countered the effects of tianeptine overdoses supports the role of opioids in tianeptine actions. Last, the metabolism of tianeptine also differs from other TCAs. Most TCAs are metabolized by the hepatic cytochrome P450 system. However, tianeptine is not metabolized via this route making it less prone to drug-drug interaction.

➢ *Tianeptine use is frequently associated with a toxicity response comprised of characteristics adverse signs and symptoms*

- Lauhan R, Hsu A, Alam A, Beizai K. Tianeptine abuse and dependence – Case report and literature review. Psychosomatics epub July 19, 2018

- Pillai R, Zakhary B, Mukherjee V. Management of respiratory depression from tianeptine overdose with naloxone. Am J Respir Crit Care Med 193: A5344, 2016

- Proenca P, Teixeira H, Pinheiro J, Monsanto PV, Vieira DN. Case report: Fatal intoxication with tianeptine (Stablon®). Forensic Sci Int 170: 200–203, 2007

- Wagstaff AJ, Ormrod D, Spencer CM. Tianeptine: A Review of its Use in Depressive Disorders. CNS Drugs 15 (3): 231-259, 2001

- Zahran TE, Schier J, Glidden E, Kieszak S, Law R, Bottei E, Aaron C, King A, Chang A. Characteristics of tianeptine exposures reported to the National Poison Data System - United States, 2000 – 2017. MMWR 67(30): 815-818, 2018

  The findings from initial clinical investigations of tianeptine and from the early use of this substance as a prescription drug suggested that tianeptine was well-tolerated and associated with fewer side effects than other established antidepressants. However, subsequent findings that emerged over time on the use of tianeptine revealed potential problems exist after exposure due to the toxicity of tianeptine. A range of adverse reactions to tianeptine are described in the published literature and are associated with several physiological systems in the body. The systems that are most commonly affected are the nervous,

[15] Tianeptine acts at the δ-opioid receptor with much lower potency than it acts at the μ-opioid receptor.

cardiovascular and gastrointestinal systems. The clinical signs and symptoms associated with nervous system include miosis (or pinpoint pupils), drowsiness, sleep disturbances or changes in dreaming, agitation and confusion along with alterations in mental state exhibited by feelings of euphoria, drug cravings and impulsive behavior. The adverse effects in the cardiovascular system include tachycardia, hypo- or hypertension, arrhythmia and conduction delays. Gastrointestinal disturbances include nausea, vomiting and constipation or diarrhea. Other adverse outcomes of exposure to tianeptine noted are headache, dizziness, anorexia, weight loss, dysuria, abdominal pain, dry mouth and lethargy. The reported adverse effects of exposure to tianeptine tend to emerge at high therapeutic doses, or at doses above the therapeutic dose levels, and sometimes involve concurrent exposure to another agent.[16] High dose exposures above the recommended therapeutic treatment levels have been reported more often in recent years, especially with the increased access to tianeptine and its use outside those as an approved drug for specific medical therapeutic purposes. Next, fatal poisonings have been documented after overdose exposure to tianeptine. These reactions have been noted to be due to both intentional and unintentional intoxications. The toxic effects seen after this type of exposure include the initial responses of lethargy, unresponsiveness or obtunded consciousness, and respiratory depression along with cyanosis and bradypnea. Other toxicity responses seen are tachycardia, and eventually cardiac, pulmonary and renal failure. Postmortem internal examinations have found tissue congestion (e.g., cerebrum and lungs) and edema. Finally, evidence suggests that some healthy individuals are consuming tianeptine for reasons outside of its clinical purpose as a therapeutic agent (e.g., antidepressant, antianxiety) and instead for its general benefits such as nootropic effects. However, investigation of the effects of tianeptine in normal, healthy individuals led to the subjects experiencing diminished cognitive (e.g., reduced emotional memory) and psychomotor (e.g., attentional vigilance to positive stimuli) skills.

➢ *Numerous case reports of adverse or hazardous reactions to tianeptine are found in the published literature*

- Bakota EL, Samms WC, Gray TR, Oleske DA, Hines MO. Case reports of fatalities involving tianeptine in the United States. J Anal Toxicol 42: 503–509, 2018

- Goodnough R, Li K, Fouladkou F, Lynch KL, Shah M, Smollin CG, Blanc PD. Notes from the Field: Toxic leukoencephalopathy associated with tianeptine misuse – California, 2017. MMWR 67: 769-770, 2018

- Le Bricquir Y, Larrey D, Blanc P, Pageaux GP, Michel H. Tianeptine – an instance of drug-induced hepatoxicity predicted by prospective experimental studies. J Hepatol 21: 771 – 773, 1994

- Pillai R, Zakhary B, Mukherjee V. Management of respiratory depression from tianeptine overdose with naloxone. Am J Respir Crit Care Med 193: A5344, 2016

- Proenca P, Teixeira H, Pinheiro J, Monsanto PV, Vieira DN. Case report: Fatal intoxication with tianeptine (Stablon®). Forensic Sci Int 170: 200–203, 2007

- Springer J, Cubała WJ. Tianeptine abuse and dependence in psychiatric patients: A review of 18 case reports in the literature. J Psychoactive Drugs 50(3): 275-280, 2018

Numerous individual adverse reaction events associated with the ingestion of tianeptine have been documented in the published literature. These case reports describe various instances of individuals experiencing harm to their health after consuming a tianeptine product. These products were taken in the form of a prescribed approved drug, or a dietary supplement or unapproved drug purchased on the internet. The published cases represented instances when the adverse

[16] This point was included to note that some tianeptine exposure cases involved concurrent exposure to other agents. However, only the adverse effects that are associated with tianeptine exposure alone, or that were determined by an evaluating clinician as being attributed to tianeptine exposure are described in this section.

reactions were severe enough that medical evaluation and treatment was sought by the tianeptine consumer, or those finding them ill or incapacitated. The medical care typically includes emergency care for poisoning, general supportive care, and/or treatment in critical care units depending on the severity of the reactions. Many case reports associated with tianeptine exposure found in the literature were first and most often documenting detrimental health effects in individuals from countries that have approved the use of tianeptine as a drug for medical treatment, and thus, allow for its marketing and sale. However, with the increased availability of tianeptine products for purchase via the internet, a recent increase in the number of adverse reaction reports for this substance are found in countries like the US where it is not approved as a drug or allowed as a dietary supplement. The latter type of purchase and use of tianeptine were found to be for self-medicating a health condition, to enhance aspects of general functioning, to use for recreational purposes, to sustain an addiction, or in a few cases, it was thought that tianeptine was used as a vehicle to commit suicide. Tianeptine-induced severe adverse responses documented tended to occur or were estimated to be at doses substantially higher than recommended therapeutic dosages. The available case reports involve individuals across a range of ages but tend to most often involve those in their twenties and thirties. Instances of fatal outcomes are included in the case reports available in the literature and include at least three fatalities associated with tianeptine exposure in the US.[17] One US death attributed to tianeptine misuse involved a 24-year old man and represents the first known case of tianeptine-induced toxic leukoencephalopathy which reflects significant brain damage. Last, another non-fatal case report suggested that tianeptine appears to have the potential to induce hepatoxicity in some individuals and is associated with a response manifested by an immune-allergic mechanism.

➢ *Tianeptine use is tied to the potential for the development of addictive behavior and associated issues of abuse and misuse*

- Lauhan R, Hsu A, Alam A, Beizai K. Tianeptine abuse and dependence – Case report and literature review. Psychosomatics epub July 19, 2018

- Springer J, Cubała WJ. Tianeptine abuse and dependence in psychiatric patients: A review of 18 case reports in the literature. J Psychoactive Drugs 50(3): 275-280, 2018

- Gupta S, Wallace R, Sloshawer J. Online sales of unscheduled pharmaceutical agents: A case report of tianeptine use in the United States. J Addic Med 11(5): 411 - 412, 2017

- Kisa C, Bulbul DO, Aydemir C, Goka E. Is it possible to be dependent to Tianeptine, an antidepressant? A case report. Prog Neuro-Psychopharmacol Bio Psych 31: 776–778, 2007

Recent evidence suggests that tianeptine has the properties of an addictive substance that can foster its misuse and abuse. These properties are characterized by the development of tolerance, the gradual increase of dosages well above typical therapeutic levels, the emergence of withdrawal symptoms upon cessation, and the failure of cessation attempts. Medical intervention such as hospitalization and treatment are often required to obtain successful withdrawal from tianeptine use. Numerous reports are found in the published literature that describe individuals that exhibited an addiction to tianeptine. This misuse and abuse of this substance often develops when the benefits seen at initial therapeutic dose levels wane and/or when a dependence on (or craving for) this substance develops. Addiction to tianeptine has been exhibited in consumers who were prescribed a drug legally by their physician for a health condition (e.g., depression, anxiety), or who self-mediated with a tianeptine dietary supplement or unapproved drug product purchased online. Some Individuals with a history of addiction to other agents appear to have an increased potential for tianeptine addiction and abuse; however, others without this history also have developed a dependence on tianeptine which lead to abuse of it. A 2018 review of published cases of tianeptine abuse and dependence indicated the average daily dose taken in these instances was approximately 1920 mg/day which is well over the

[17] In at least one of these US fatalities related to tianeptine exposure, it is possible the route of exposure to this agent was through intravenous injection.

recommended prescribed doses of between 25 and 50 mg/day. But, tianeptine doses at least as high as 3000 mg/day have been reported in individuals addicted to this agent. The signs and symptoms associated with the withdrawal from tianeptine include agitation, irritability and/or excitability, tremors, anxiety, nausea, vomiting, excessive hunger or anorexia, dry mouth, tachycardia, hyper- or hypo-tension, sweating, hot flashes, cold/flu-like symptoms, extreme weakness and/or fatigue, insomnia, dizziness, mood or emotional lability, myalgia, abdominal pain, and diarrhea or constipation. In addition, some cases of neonatal abstinence syndrome occurring after tianeptine use during pregnancy have been described. Last, some findings suggest that the opioid activity, along with effects on the dopaminergic reward pathways in the brain, may contribute to this addiction effect.

➢ *Incidence of tianeptine poisonings increasingly have been reported to established governmental reporting systems in recent years. It includes reporting systems in the US, a country where tianeptine is not an approved drug, and in Turkey, a country where it is approved for use*

- Zahran TE, Schier J, Glidden E, Kieszak S, Law R, Bottei E, Aaron C, King A, Chang A. Characteristics of tianeptine exposures reported to the National Poison Data System - United States, 2000 – 2017. MMWR 67(30): 815-818, 2018

- Durmus N, Ozbilen G, Kasap Y, Koyuncu O, Yildirim O, Artiran G, Kerman S, Aydinkarahaliloglu D. Risk Management in Tianeptine Abuse in Turkey: A National Experience. Bull Clin Psychopharmacol 23(2):149 - 154, 2013

A review by the US Centers for Disease Control and Prevention (CDC) of reports to the US National Poison Data System (NPDS) on exposures to the unapproved drug tianeptine was recently published. It summarized the nature and characteristics of all calls about tianeptine exposure made to poison control centers in the US that were reported to NPDS between 2000-2017. During this period, NDPS received 218 calls pertaining to the use of tianeptine with the most being from healthcare providers (91%) and for the ingestion of tianeptine via the oral route of exposure (84%). There has been a significant increase in tianeptine-related calls nationwide in recent years. Over the 18-year reporting period, the majority of tianeptine exposure calls (95%) to poison control centers occurred between 2014 -2017, leading the study authors to suggest issues with tianeptine use is “a possible emerging public health risk.” The nature of contact calls to poison control centers about tianeptine reflected intentional and unintentional misuse, and abuse and withdrawal reactions. The mean age for tianeptine users was 35 years old with ages ranging from 1 to 80 years old. Poison control centers reported tianeptine users were predominately males (84%). The exposures by individuals were comprised of those who consumed tianeptine only (60%; excluding withdrawal-associated calls) and those who consumed other agents (e.g., Phenibut) in addition to tianeptine. The group reporting co-exposures along with tianeptine tended to have more severe reactions. The level of care provided tianeptine users ranged from treatment in an emergency department and subsequent release to admission to a critical care unit. In assessing available information on known medical outcomes, CDC classified 54% of those with tianeptine-only exposures as having “moderate outcomes” which CDC defines as pronounced, prolonged symptoms of a systematic nature requiring some form of medical treatment but returning to pre-exposure state with no significant residual effects. No poison control center tianeptine-related contact calls reported deaths in US between 2000-2017.

Next, another established US reporting system has received adverse event reports about tianeptine-containing products. The FDA Center for Food Safety and Applied Nutrition (CFSAN) maintains a database of information on adverse event and product complaint reports submitted to FDA by consumers of products

including dietary supplements.[18] This voluntary reporting system, CFSAN Adverse Event Reporting System or CAERS, has received four direct complaints between 2016 – 2018 about tianeptine-based products taken orally.[19] They were reported under the "voluntary dietary supplement report" profile and were categorized as adverse event reports. The consumer complainants were all male and ranging in age between 28 and 47 years old. Two of the consumers provided some information on the content of and/or dosage of use for the tianeptine products. One of these consumers indicated the tianeptine product that he ingested contained 531 mg, and the other consumer ingested a product that contained 120 mg at a dosage up to 3 g per 3 hours (or about 5 times a day).[20] The reasons for using these products noted by the four CAERS consumer complainants included energy, mood, anxiety, pain and depression along with the product being an alternative to Kratom. Some of the descriptions provided in the reports for inquiries about the "event," "problem" and/or "outcome" comprised the following: misuse or abuse references like opioid effects along with addictive, development of tolerance, lead to hard drug use, and withdrawal; symptoms and illness status like slow breathing, life-threatening, mental illness, disability or incapacity, and general health deterioration; and feelings or experiences like being high, hooked on, and dangerous with reference to product use, and intense, rage, suicidal and depression with reference to withdrawal of product use. No reference to obtaining medical treatment for their tianeptine-related reactions were noted by consumer complainants in the available CAERs reports. In sum, the findings from adverse event reports to the US CAERS reveal the occurrence of adverse event effects associated with tianeptine product consumption in some instances and suggest the presence of addiction and withdrawal responses potentially tied to this exposure.[21]

Last, a published paper described an examination of several governmental pharmacovigilance databases (e.g., Turkish Pharmaceuticals Track and Trace System) through 2012 by the Turkish Medicines and Medical Devices Agency, along with a review of reports to the Agency's Risk Management Department, for information related to adverse drug event reports for tianeptine, an approved drug in Turkey. Also assessed were databases that contain data on market share of antidepressants purchased with and without a prescription in various Turkish cities. An increase in adverse event reports has been seen over the years evaluated. It included three individual fatal cases (all in men from 35 – 51 years old) between 2011 and 2012 which were associated with tianeptine abuse. An increase in addictive behaviors related to the use of tianeptine in Turkey is also suggested.

Review and Evaluation conducted by
[redacted] MS, PhD
Senior Toxicologist
Toxicology Team, DBGNR, OFAS

[18] The information on the nature and content of these CAERS reports are not published in the scientific literature nor available for outside review. This is a summary of information derived directly from the submitted reports to FDA.

[19] CAERS received a fifth report (dated 2015) that was forwarded to FDA by the US Consumer Product Safety Commission (CPSC) about a hospitalized 33-year old male. However, five drugs or agents in addition to tianeptine were listed as consumed by this individual. It was not clear from the CPSC incident report whether these agents were consumed at separate times or in combination. Thus, the information from this report was not included along with the other CAERS reports about tianeptine use that is described and discussed here.

[20] Information on the specifics of what comprised the mg content of the noted tianeptine products was not provided or available in the CAERS reports.

[21] The review, evaluation and summarization of the available CAERS information on tianeptine product use that is described here was performed by the author of this document. Hence, it does not necessarily reflect the analysis or conclusions by CFSAN staff responsible for the CAERS database, or the CFSAN office responsible for the regulation of dietary supplements (Office of Dietary Supplements Programs).