November 7, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Via Email: oira_submission@omb.eop.gov
Fax: 202–395–7285

RE: Docket No. FDA-2016-N-2523 “Request for Comment on the Status of Vinpocetine”

Dear FDA Desk Officer,

The Natural Products Association (NPA) is submitting this letter as formal comments to Docket No. FDA-2016-N-2523, “Request for Comment on the Status of Vinpocetine” published in the Federal Register on September 7, 2016 (81 FR 61700), regarding the agency’s initiation of an unprecedented administrative proceeding under 21CFR 10.25(b) to determine the regulatory status of vinpocetine (ethyl apovincaminate). NPA was founded in 1936 to promote and protect the unique values and shared interests of retailers and suppliers of natural nutritional foods and natural products. We are the oldest and largest trade association in the natural products industry representing over 1,400 members accounting for almost 10,000 retail, manufacturing, wholesale, and distribution locations of natural products, including foods, dietary supplements, and health/beauty aids. Furthermore, NPA is the leading trade association for dietary supplements. NPA is a non-profit 501(c) (6) association whose mission is to advocate for the rights of consumers to have access to products that will maintain and improve their health, and for the rights of retailers and suppliers to sell these products. As the natural products trade association, the NPA, in addition to our members, maintains a significant
interest in the FDA’s use of an administrative proceeding to attempt to alter the regulatory status of an FDA-acknowledged dietary ingredient for use in dietary supplements.

**Background on Vinpocetine**

Vinpocetine is often described as a semi-synthetic alkaloid discovered during the late 1960s. It is typically derived from carboline alkaloids found in periwinkle (*Vinca minor*) leaves and it is similar in structure and pharmacology to a very closely related analog\(^1\) isolated from *Tabernaemontana rigida, Tabernaemontana riedelii*, \(^2\) *Vinca erecta*\(^3\) and *Vinca minor*.\(^4,5\) The first clinical studies on the cerebrovascular hemodynamic properties of vinpocetine occurred in the 1970s, and it was first introduced as a drug under the trade name Cavinton\(^\circledast\) in 1978 by pharmaceutical formulator Gedeon Richter Nyrt in Hungary. The scientific literature contains numerous human clinical studies and animal investigations on the pharmacological and biochemical actions of vinpocetine. These include antioxidant effects,\(^6\) menopause, eye disorders, kidney impairment, stroke,\(^7,8\) uncontrolled micturition, reductions in platelet

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\(^{1}\) Apovincamine is the methyl ester of (3α, 16α)-eburnamenine-14-carboxylic acid and is a constituent in several different botanicals, thereby fitting under 201(ff)(1)(F) of the Federal Food, Drug, and Cosmetic Act. Vinpocetine, in comparison, is the ethyl ester of (3α, 16α)-eburnamenine-14-carboxylic acid. Ester bonds are cleaved by esterases in the body and would therefore result in (3α, 16α)-eburnamenine-14-carboxylic acid as the active moiety for either vinpocetine or apovincamine.


aggregation,\(^9,10,11\) antiulcer activity, phosphodiesterase-1 inhibition,\(^12\) cerebrovascular vasodilation,\(^13,14\) hearing defects of neurological origin\(^15,16,17,18,19\) and other brain disorders.\(^20,21\)

Vinpocetine is also known as 14-Ethoxycarbonyl-(3alpha, 16alpha-ethyl)-14,15-eburnamine, apovincaminate acid, Cavinton\(^\circledR\), cezayirmeneksesi (Turkish), Crioceras longiflorus, ethyl apovincaminate, Eusenium\(^\circledR\), Intelectol\(^\circledR\), kavinton, myrtle vincapervinc, periwinkle, RGH-4405, TCV-3b, vinRx, vintoperol, and Voacanga Africana. It has since been used widely in Japan, Germany, Russia, Poland, and Hungary for the treatment of cerebrovascular-related pathologies.\(^22\) Vinpocetine has never been approved for use as a drug in the United States (U.S.) by the U.S. Food and Drug Administration (FDA) for any condition. It has been lawfully marketed in the U.S. as a dietary ingredient for use in dietary supplements, a category of food in the U.S. Vinpocetine has become popular for its protective effects on the nervous system and therefore has been marketed for brain health, boost memory, support attention, promote alertness, and other structure function claims in the U.S. over the past 19 years.

Regulatory Status of Vinpocetine in the U.S.

Vinpocetine has never been an approved drug in the U.S. It has been lawfully marketed as a dietary ingredient for use in dietary supplements. In fact, vinpocetine holds the distinction of having five (5) New Dietary Ingredient (NDI) notifications filed with FDA’s Center for Food Safety and Applied Nutrition (CFSAN). By 1994, companies manufacturing and distributing dietary ingredients for use in dietary supplements had to submit NDI notifications to FDA CFSAN if the ingredient was intended to be sold in a dietary supplement and was something never before introduced into the diet. The first submission to the FDA docket for NDIs (FDA-95S-0316) after its creation occurred in July 1995. Part of FDA’s review of a submitted NDI is to investigate its current regulatory status as a drug. FDA NDI team members will look up an ingredient in FDA’s Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) and report back as to whether an Investigation New Drug (IND), New Drug Application (NDA), or orphan drug has ever been filed for the ingredient and whether it is still active or inactive. Because FDA classified its first vinpocetine NDI submission in 1997 as “filed without comment”, any DARRTS query by FDA’s James Tanner and Robert J. Moore would have yielded either a null return or an “inactive” drug application status. While FDA may have received an IND application for the compound known as vinpocetine at some point (NPA is unable to confirm), the IND status in FDA’s DARRTS would have indicated vinpocetine’s status as “inactive” at the time of the evaluation of all five NDI submissions. An alternate explanation is that FDA personnel failed to perform such a DARRTS search. In any case, FDA has classified five NDI notifications to date as AKL (“acknowledgement”) letters, meaning vinpocetine was filed without comment each time. These five vinpocetine submissions also do not suggest that they were pure natural extracts or metabolites from a botanical source.

- Amrion, Inc. (filed July 8, 1997)
- Leiner Health Products (filed October 20, 1998)
- Leiner Health Products (filed March 24, 1999)
- General Nutrition Corporation (April 16, 1999)
- Pharmavite Corporation (May 12, 1999)
By submitting five separate NDI notifications for vinpocetine, the FDA had a total of 375 days (75 days x 5 submissions) to review whether it was a drug ingredient and how it fits under the definition of dietary ingredient in 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act (FFDCA). FDA’s acknowledgement of these five NDIs suggests that 1) synthetically made vinpocetine fits under the definition of a dietary ingredient in Section 201(ff)(1) [21 USC §321(ff)(1)], 2) vinpocetine submissions contained reasonable expectations of safety to the consumer, and 3) vinpocetine can be lawfully marketed and sold in the U.S. To date, vinpocetine contains 19 years of lawful historical safe use in the U.S. alone as a food and 38 years of safe use in Europe as a drug/functional food.23 FDA and the European Union considers 25 years of widespread use to be the minimum to establish a history of safe use, according to their definition.24,25 As NPA is unaware of any chemical changes to vinpocetine over the past 38 years, this dietary ingredient has demonstrated sufficient historical safe use worldwide and domestically as a lawfully marketed dietary ingredient for use in dietary supplements.

Vinpocetine Fits Under 201(ff)(1)(F) in Addition to 201(ff)(1)(E) of the FFDCA

Apovincamine, a constituent of *Tabernaemontana rigida*, *Tabernaemontana riedelii*, *Vinca erecta*, and *Vinca minor*, is the methyl ester of (3α, 16α)-eburnamenine-14-carboxylic acid is an analog of vinpocetine, which is the methyl ester of (3α, 16α)-eburnamenine-14-carboxylic acid. Both esters would be cleaved by esterases in the human body, resulting in (3α, 16α)-eburnamenine-14-carboxylic acid as the active moiety or relevant article (see Figure 1.). Therefore, the active moiety of vinpocetine, (3α, 16α)-eburnamenine-14-carboxylic acid, is a metabolite of apovincamine, a botanical constituent, and therefore vinpocetine would fit under

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23 Most foreign governments do not contain the U.S. category of food known as dietary supplements. These products are typically regulated as drugs or functional foods in those countries.
25 See, e.g., the definition proposed in the European Union: “‘[H]istory of safe food use in a third country’ means that the safety of the food in question is confirmed with compositional data and from experience of use and continued use for at least 25 years in the customary diet of a large part of the population of a country.” Offic J Eur Union C 122 E (May 11, 2010); p. 38-57.
both 201(ff)(1)(E) and 201(ff)(1)(F), based upon FDA’s definition of “active moiety” in its NDI Draft Guidance.\(^{26}\) FDA stated that under 21 CFR 316.3(b)(2), “active moiety” means “the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.”\(^{27}\)

![Figure 1. Apovincamine and Vinpocetine](image)

**FDA Wrote “NDL” Letters in Response to NDI Notifications for Other Ingredients in 1999**

NDL or “not a dietary ingredient” letters have been filed by FDA as early as 1999. In NDI #050 (report 43), a notifier submitted a dossier for acetyl-homotaurine (acamprosate) on March 11, 1999. In FDA’s response letter to Chemtech Pharmics, Inc., FDA wrote the following:

> “The definition (of a dietary ingredient) excludes an article that is approved as a new drug under section 505 of the Act or an article authorized for investigation as a new drug, for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was


\(^{27}\) See also 21 CFR 314.108(a).
not before such approval or authorization, marketed as a dietary supplement or as a food (21 U.S.C. 321(ff)(3)(B)).

Acamprosate is the subject of substantial clinical studies being conducted in the United States to determine if it is a safe and effective drug treatment for alcohol dependence. The existence of these substantial clinical studies has been made public. Therefore, acetyl-homotaurine, or acamprosate, is excluded from being a dietary supplement under 21 U.S.C. 321(ff)(3)(B).

A product containing acetyl-homotaurine that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease or is intended to affect the structure or function of the body is a drug as described in 21 U.S.C. 321(g)(1). Such a product is also a new drug, as defined in 21 U.S.C. 321(p), which requires FDA approval under 21 U.S.C. 355(a) prior to marketing. The marketing of new drugs without an approved new drug application is prohibited under 21 U.S.C. 331(d).”

In order for CFSAN to compose this letter, a review in DARRTS would have been performed during a NDI legal status review to determine the regulatory status of acetyl-homotaurine as a drug, which in turn affected how this ingredient fit under 201(ff)(1) of the FFDCA. FDA had the opportunity to compose a similar letter for vinpocetine during this same timeframe, but FDA apparently lacked the necessary triggers with vinpocetine in their internal policies to similarly kick vinpocetine out as a dietary ingredient within the meaning of 201(ff)(3)(B) [21 U.S.C. §321(ff)(3)(B)].

NPA Supports the Lawful Marketing of Vinpocetine in the U.S. and Possesses Sufficient Historical Use

When vinpocetine was first notified to FDA CFSAN in 1997, this ingredient contained 19 years of historical safe use in Europe and Asia. Therefore, the manufacturers/distributors of
vinpocetine made the correct choice to submit an NDI notification within the meaning of sections 413 [21 U.S.C. §350b] and 402(f)(1)(B) [21 U.S.C. §342(f)(1)(B)]. Furthermore, the authors of those NDI submissions correctly furnished FDA with other evidence of safety to support a “reasonable expectation of safety” rather than rely solely on historical use. Today, vinpocetine contains over 19 years of safe historical use in the U.S. as a food and over 38 years of safe historical use as a functional food/drug in Europe and Asia. Therefore, vinpocetine possesses greater than the 25 years adopted by both FDA and the European Union that is required for safe historical use. As a result, any future NDI submissions from other notifiers would only have to provide this historical safe use in their NDI submissions to the agency in lieu of expensive “other evidence” in animal studies to satisfy “reasonable expectation of safety.”

**FDA’s Decision to Tentatively Conclude Vinpocetine is Not a Dietary Ingredient**

While FDA employees have been quoted that FDA is not placing a ban on vinpocetine but rather soliciting company information on the ingredient, it is clear from their intent that FDA currently concludes that the dietary ingredient, in the absence of any additional information provided to them, is not a dietary ingredient for use in dietary supplements. FDA wrote in their administrative proceedings notice that “we request comments on our tentative conclusion that vinpocetine is not a dietary ingredient and is excluded from the definition of dietary supplement in the Federal Food, Drug, and Cosmetic Act (FD&C Act).” NPA supports vinpocetine as a lawfully marketed NDI five times over. Vinpocetine would at the very least fit under section 201(ff)(1)(E) as “a dietary substance for use by man to supplement the diet by

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28 21 U.S.C. §350b – New dietary ingredients. (1) In General. A dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 342(f) of this title unless it meets one of the following requirements:

1. The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.

2. There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the Secretary with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.
increasing the total dietary intake.” FDA also questions whether vinpocetine is a dietary ingredient under 201(ff)(3)(B)(ii) of the FD&C Act because it was authorized for investigation as a new drug in 1981. In FDA’s interpretation of “authorized for investigation as a new drug”, FDA states that this “authorization” occurs in the following manner.

“An article becomes ‘authorized for investigation as a new drug’ after the sponsor has submitted an investigational new drug application (IND) to FDA and the IND has gone into effect. Unless FDA notifies the sponsor that the clinical investigation described in the IND has been placed on clinical hold, the IND goes into effect 30 days after being submitted to FDA (21 CFR 312.40(b)). Although FDA will not disclose the existence of an IND that has not previously been publicly disclosed or acknowledged (21 CFR 312.130), the existence of the 1981 IND for vinpocetine was publicly disclosed in the press no later than 1986.”

FDA does not elaborate on what happens in the case that the IND becomes “inactive”. INDs are not presumed to be active forever upon “authorization” as FDA’s interpretation would imply. In the case of vinpocetine, the vinpocetine IND, publicly disclosed in 1986, went inactive and was no longer “in effect”. This is presumably the reason why FDA responded to the vinpocetine NDI with an AKL letter (“filed without comment”), which is the highest level of support FDA can send in response to a notifier’s NDI notification. Therefore, NPA does not support FDA’s decision to re-open the regulatory status of vinpocetine and potentially “ban” it from being sold as a dietary ingredient for use in a dietary supplement. NPA believes FDA personnel made the correct regulatory designation for vinpocetine in 1997.

FDA Authority to Re-Evaluate Vinpocetine’s Regulatory Status as a Dietary Ingredient

NPA believes FDA does not have the regulatory authority to re-evaluate vinpocetine as a dietary ingredient after it has been concluded to be an acknowledged NDI. In his October 25, 2016 letter to FDA Commissioner Robert Califf, Senator Orrin Hatch stated that “this is the first
time that FDA has attempted to pull a product for a definitional reason instead of a public health concern”. If FDA enforces their tentative conclusion and retailers refuse to pull these products, FDA would pull products from store shelves over a definitional reason. Senator Hatch further states that “[b]y removing a product from market without safety concerns, FDA would be taking a precedential step that could shake the confidence that manufacturers maintain in the FDA process.” NPA interprets that to ask why a manufacturer or distributor would want to engage the NDI process if FDA will revisit whether it fits under 201(ff)(1) at a future date. FDA believes more NDIs should be submitted to them, but this administrative proceedings, while puzzling on its own merits, would not lead to increased notifications to the agency.

**FDA Failed to Submit an Economic Impact Analysis to the Office of Management and Budget Regarding this Cost to the Industry and Regulatory Alternatives**

FDA failed to evaluate the economic impact under Executive Order 13563 and 12866, the Regulatory Flexibility Act (5 U.S.C. §601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 13563 and 12866 direct agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety effects, distributive impacts, and equity). Executive Order 13563 emphasizes the importance of quantifying both costs and benefits, of reducing costs, of harmonizing rules, and of promoting flexibility. If the regulatory action has been designated “economically” significant under section 3(f)(1) of Executive Order 12866, the action would then have to be reviewed by the Office of Management and Budget. The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 M or more (adjusted annually for inflation) in any one year.”
Senator Hatch’s letter to Commissioner Califf similarly questioned whether the Office of Management and Budget did a full review of the economic impact of enforcing their new tentative conclusion in FDA’s administrative proceeding. Citing Executive Order 12866, Hatch states that the Office of Information and Regulatory Affairs of the Office of Management and Budget (OMB) should follow a transparent process when a federal agency makes a determination that is significant. Vinpocetine has a large footprint in the dietary supplement market and serves as a component in many common products. Today, more than 377 brands of supplements contain vinpocetine, according to the Natural Medicines Comprehensive Database. NPA believes this estimate of the number of brands selling vinpocetine today constitutes “economically significant” to warrant an OMB review.

**NPA Urges FDA to Use Their Mandated Authority Based Upon Safety**

Section 4 of the Dietary Supplement Health and Education Act of 1994 (DSHEA), cosponsored by nearly two-thirds of Congress and passed unanimously, provides pathways for withdrawing dietary ingredients based on safety concerns. However, FDA cites no unreasonable risk of illness or injury to public health in the administrative proceeding. Therefore, this notice creates uncertainty in the market as to what steps manufacturers can take to sell safe products. In order to ensure consumer safety, FDA has the authority under DSHEA to conduct product reviews and post-marketing assessment when safety concerns arise. FDA has access to adverse events submitted through Medwatch to either the Adverse Events Reporting System (AERS) of at the Center for Drug Evaluation and Research (CDER) or the CFSAN Adverse Events Reporting System (CAERS). If there is a safety signal that warrants enforcement of this acknowledged dietary ingredient, NPA supports this activity as per FDA’s regulatory authority. NPA is unaware of any adverse event to warrant any enforcement action on vinpocetine.

NPA also recognizes that FDA can inquire from manufacturers of vinpocetine whether they have ever submitted an NDI notification for vinpocetine. NPA can charge a company with Section 402(f)(1)(B), an adulteration based upon a failure to file an NDI notification; however,

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this would be unprecedented because FDA has historically granted enforcement discretion regarding Section 402(f)(1)(B). FDA typically only charges this Section in the event of a failure to file an NDI notification AND a safety concern. However, NPA would be supportive of FDA using 402(f)(1)(B) as a form of intellectual property (IP) protection for those firms that have submitted an NDI as required by statute, in contrast to firms that fail to submit. If FDA directs all vinpocetine manufacturers/distributors to file an NDI notification, it would lead to greater numbers of NDI submissions, provide greater transparency in the marketplace, eliminate “piggy back” NDI rides, and encourage all companies to invest in safety of their ingredient. NDI submissions, while statutorily required, do not allow companies to recoup their investments when NDIs are not enforced even-handedly across the board by FDA. Regarding vinpocetine, the cost to submit by other manufacturers would be minimal. A notifier would likely only require historical safe use in prior NDI submissions to satisfy reasonable expectation of safety because the ingredient has enjoyed 38 years of safe use worldwide. In the case of vinpocetine, NPA is not aware of any basis as to why a company would not submit an NDI as per the statute since the required elements of this submission would not incur large costs.

Conclusions

In the Request for Comment on the Status of Vinpocetine, FDA has altered its conclusion that vinpocetine is a dietary ingredient, and that it should no longer be a covered substance under the FFDCA. Vinpocetine fits under 201(ff)(1)(F) or 201(ff)(1)(E) of the FFDCA. The active moiety of vinpocetine, (3α, 16α)-eburnamenine-14-carboxylic acid, upon esterase cleavage, is a metabolite of the botanical constituent apovincamine. Taking such a position to ban the sale of vinpocetine when used as a dietary ingredient for use in a dietary supplement in the absence of any safety concern is unprecedented. DSHEA provides a regulatory framework for banning and withdrawing dietary ingredients from the market based upon safety concerns. In the absence of any risk of illness or hazard to public health, this administrative proceeding creates a new pathway to place a ban on acknowledged ingredients and introduces considerable uncertainty and confusion as to what steps manufacturers must comply with in order to sell safe products.
FDA has the authority to conduct safety reviews, evaluate adverse events, and classify their causality as per the Dietary Supplement and Nonprescription Drug Consumer Act of 2006 using the Council for International Organizations of Medical Sciences (CIOMS) guidelines for assigning causality. FDA can also inquire whether a manufacturer has submitted an NDI notification for a dietary ingredient and render a product adulterated if they failed to file an NDI notification. However, the FDA has reviewed NDI notifications for vinpocetine in 1997, 1998 and three times in 1999. Each time, FDA had 75 days to conduct safety reviews, regulatory status checks in DARRTS, and opine on whether vinpocetine fits as a dietary ingredient under 201(ff)(1) of the FFDCA. Each 75-day evaluation was an opportunity to raise concerns about whether vinpocetine was a dietary ingredient as per DSHEA, yet the FDA did not object to this dietary ingredient during any of the five reviews, allowing it to proceed to the market each time. The FDA had a total of 375 days to make a determination as to the regulatory status of vinpocetine, while giving industry only 60 days to respond to their tentative conclusion that it is not a dietary ingredient.

Further, given that OMB did not perform a full review of the economic impact of this notice and its regulatory ramifications, NPA urges FDA to submit their economic impact analysis to OIRA of the OMB in order to follow a transparent process in accordance with Executive Order 12866. NPA, in addition to Senator Hatch, is calling on FDA to complete a thorough economic impact analysis in its second set of comments in response to FDA’s tentative conclusion to reverse the regulatory status of vinpocetine and ban this five-time acknowledged dietary ingredient for use in dietary supplements. NPA requests a year to allow time for industry to respond and for FDA to develop an economic impact analysis of the impact of this decision. NPA also requests that FDA withdraw its administrative proceeding on vinpocetine during this one-year period as FDA had over a year to figure out vinpocetine’s status between 1997 and 2000. Given that FDA has had five opportunities to make this reversal on an acknowledged dietary ingredient, the agency signaled that the product was lawful and could be sold in the U.S.
NPA thanks FDA for the opportunity to comment twice on this administrative proceedings to re-evaluate the regulatory status of vinpocetine and looks forward to working with the Agency.

Sincerely,

Daniel Fabricant, Ph.D.
CEO, Executive Director
Natural Products Association