



200 Cottontail Lane
Somerset, NJ, USA 08873
Tel: 732 584 5231
Fax: 732 652 7813
www.medicurepharma.com

0672 7 NOV 30 A9:55

November 28, 2007

Division of Dockets Management
Food and Drug Administration
Room 1061, HFA-305
5630 Fishers Lane
Rockville, Maryland 20852

Re: **CITIZEN PETITION TO PROHIBIT THE MARKETING OF DIETARY SUPPLEMENTS CONTAINING PYRIDOXAL 5'-PHOSPHATE**

Dear Sir or Madam:

Medicure Pharma Inc. ("Medicure") submits this citizen petition pursuant to sections 301(a), 301(v), 402(f), and 413 of the Food, Drug, and Cosmetic Act ("FDCA") to request that the Commissioner of Food and Drugs (the "Commissioner") take the actions described below regarding the unlawful marketing of dietary supplements containing pyridoxal 5'-phosphate ("P5P"). 21 U.S.C. §§ 331(a), 331(v), 342(f), 350b.

Medicure is a drug discovery and development company focused on developing innovative, effective therapeutics for unmet needs in the field of cardiovascular medicine. Medicure was founded in 1997 by the renowned cardiovascular researcher Naranjan S. Dhalla, Ph.D., from the Institute of Cardiovascular Sciences, St. Boniface General Hospital Research Centre, University of Manitoba, and by Albert D. Friesen, Ph.D., who is also the President and Chief Executive Officer. Medicure is now engaged in substantial clinical investigations to develop, under an investigational new drug ("IND") exemption, a drug product known as MC-1.

The active ingredient in MC-1 is P5P. Nevertheless, Medicure has become aware that a number of companies are marketing dietary supplements in the United States that contain P5P. These dietary supplements are adulterated and are being unlawfully marketed. As discussed below, P5P is a new dietary ingredient requiring a 75-day pre-market notification to the Food and Drug Administration ("FDA" or the "agency"). See 21 U.S.C. § 350b(a)(2). To our knowledge, no such notification has ever been provided to the agency.

Perhaps more importantly, dietary supplements containing P5P were never lawfully marketed prior to the date that Medicure's IND for P5P became effective and the company was authorized to conduct clinical investigations on the drug. The Dietary Supplement Health and Education Act of 1994 ("DSHEA") specifically provides for enforcement action in such situations, to protect the significant investment that companies like Medicure are required to make to gain FDA approval of new drugs. It is critical that FDA take the actions requested below to remove from the marketplace dietary supplements containing P5P. The continued unlawful marketing of such products threatens to vitiate the market for Medicure's innovative drug product and undermine our incentive to continue the development of MC-1.

2007 P-0466

CP 1

I. Actions Requested

Medicure respectfully requests that the Commissioner:

1. Declare that all dietary supplements containing P5P are adulterated under the FDCA and are being unlawfully marketed; and
2. Take immediate enforcement action to remove such products from the marketplace; or,
3. If FDA declines to take immediate action, initiate a rulemaking to exclude such products from the definition of a dietary supplement, under sections 201(ff) and 701(a) of the FDCA. 21 U.S.C. §§ 321(ff), 371(a).

II. Statement of Grounds

A. Medicure Has Invested Significantly In The Development Of P5P, A Novel Cardioprotective Treatment Intended To Address Unmet Medical Needs.

Medicure is currently engaged in substantial clinical investigations to assess the cardiovascular benefits of P5P, the active ingredient in MC-1. P5P is a naturally-occurring molecule and an active metabolite of pyridoxine (commonly referred to as vitamin B6). In addition to pyridoxine, the vitamin B6 family includes other substituted pyrimidine compounds, pyridoxal and pyridoxamine, as well as the other phosphorylated forms, pyridoxine phosphate and pyridoxamine phosphate.

Based on Medicure's preclinical and clinical studies, P5P appears to be a powerful cardioprotective drug with the potential to treat a variety of cardiovascular diseases. If ultimately approved, MC-1 stands to be a first-to-market product in a new class of drugs that will reduce cardiovascular events, such as myocardial infarctions, associated with ischemia and/or ischemia reperfusion injury in patients experiencing percutaneous coronary interventions (angioplasty), coronary artery bypass graft ("CABG") surgery, and acute coronary syndrome. FDA awarded MC-1 Fast Track designation in September 2005, reflecting the drug's potential to address important unmet medical needs.

Medicure submitted its IND application for P5P on November 23, 2001, and disclosed the existence of the IND, and Medicure's subsequent initiation of clinical investigations, on November 28, 2001.¹

¹ See, e.g., *Medicure Makes FDA Filing for Phase II Clinical Trial of MC-1*, Medicure Press Release (Nov. 28, 2001) (attached at Tab 1); see also D. E. Kandzari, et al., *Reduction of Myocardial Ischemic Injury Following Coronary Intervention (The MC-1 to Eliminate Necrosis and Damage Trial)*, Am. J. Cardiol. 2003; 92: 660-64 (attached at Tab 2).

A publicly traded company, Medicure has kept its investors and the public continually informed regarding the progress of its clinical investigations throughout the development of MC-1.²

Clinical research on the drug has been extensive, and includes the following:

- * A randomized, placebo-controlled, blinded Phase II study (led by Duke Clinical Research Institute, "DCRI"), which evaluated the extent to which P5P mitigates damage to the heart muscle following elective percutaneous coronary intervention in 60 patients at increased risk for cardiac damage.
- * A randomized, placebo-controlled, double-blind Phase II study (led by DCRI and Montreal Heart Institute, "MHI") in 901 patients designed to evaluate the potential of the drug to reduce cardiovascular events associated with ischemia and/or ischemia reperfusion injury in patients undergoing CABG surgery.
- * A randomized, placebo-controlled, double-blind Phase III study in 3,000 patients undergoing CABG surgery at approximately 130 cardiac surgical centers throughout North America and Europe (led by DCRI and MHI).
- * A randomized, placebo-controlled, double-blind, parallel group, crossover Phase II study in 120 patients with co-existing type II diabetes and hypertension.³

B. Dietary Supplements Containing P5P Are Adulterated And Unlawfully Marketed.

Under DSHEA, a dietary supplement is defined as a product that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of the previous ingredients. Dietary supplements may not be represented for use as conventional foods or as the sole items of a meal or the diet, and must be labeled as dietary supplements. *See* 21 U.S.C. § 321(ff). They are also subject to good manufacturing practice requirements, *see* 21 U.S.C. § 342(g), and limitations on promotional and labeling claims. *See* 21 U.S.C. § 343(r).

² *See, e.g., Medicure Announces Positive Results From Phase II Trial on MC-1*, Medicure Press Release (Jan. 14, 2003) (attached at Tab 3); *Medicure Receives FDA Approval for Phase II MC-1 Trial*, Medicure Press Release (Jan. 9, 2002) (attached at Tab 4).

³ To date, Medicure's investment in developing MC-1 as an innovative treatment for ischemia and/or ischemia reperfusion injury has exceeded \$60 million. Enrollment in the Phase III, "MEND-CABG II" study has recently been completed and data analysis is ongoing. Medicure is expecting to file a new drug application in the second half of 2008.

In addition, a dietary supplement that contains a “new dietary ingredient” (defined as a dietary ingredient that was not marketed in the United States before the October 15, 1994, enactment of DSHEA, *see* 21 U.S.C. § 350b(c)) must meet one of the following two requirements:

1. The dietary supplement must contain only dietary ingredients that 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; or, if not
2. The manufacturer or distributor must, at least 75 days before the product is introduced or delivered for introduction into interstate commerce, submit to FDA information, including any citation to published articles, that is the basis on which the manufacturer or distributor has concluded that the dietary supplement is reasonably expected to be safe when used under the conditions recommended or suggested in the product’s labeling.

21 U.S.C. § 350b(a). Unless one of these requirements is met, a dietary supplement containing a new dietary ingredient is adulterated, and its introduction into interstate commerce is prohibited. *See* 21 U.S.C. §§ 331(a), 331(v), 342(f).

1. P5P Is A New Dietary Ingredient Requiring Either Presence In The Food Supply As An Article Used For Food Or 75-Day Pre-Market Notification.

It is not our intention to dispute whether P5P, a naturally-occurring molecule in the vitamin B6 family, qualifies as a dietary ingredient. *See* 21 U.S.C. § 321(ff). To Medicare’s knowledge, however, P5P was not marketed before October 15, 1994. To determine the earliest date that a dietary supplement containing P5P may have been marketed, Medicare and outside consultants searched numerous sources, including back issues of the Physicians’ Desk Reference for dietary supplements, Westlaw and Lexis databases, and various trade press sources, in addition to conducting general Internet searches. The earliest evidence that Medicare has discovered of the marketing of a dietary supplement containing P5P is an October 28, 1996, “Product Alert” from Marketing Intelligence Service Ltd. It describes the marketing of a non-prescription sleep aid being sold under the “Schiff” name, and lists the product as containing a variety of ingredients, including “pyridoxal 5-phosphate.”⁴

P5P also appears on a list of so-called “grandfathered” pre-1994 dietary ingredients compiled by the Council for Responsible Nutrition (“CRN”) in 1998, based on a different list drafted by the National Nutritional Foods Association.⁵ However, the list is not a reliable source for information regarding

⁴ Attached at Tab 5. Medicare has no independent knowledge of this product, and thus does not concede that it actually was marketed in 1996, or that its marketing would satisfy the requirements of 21 U.S.C. § 350b(c).

⁵ Attached at Tab 6. This list was submitted to FDA in response to a pending citizen petition regarding the status of dietary supplements containing pyridoxamine, a different molecule in the vitamin B6 family. *See* Docket No. 2005P-0305.

what ingredients were marketed before enactment of DSHEA. It merely identifies P5P, providing no documentation of the basis for that listing, and no indication of what company suggested that P5P be included. CRN itself recognized the limited value of the list, including a disclaimer that the list "is compiled solely for reference purposes and does not constitute verification that any specific dietary ingredient was or was not marketed as a dietary supplement before October 15, 1994."

FDA has previously recognized the minimal utility of the CRN list, specifically determining that a dietary ingredient's appearance on the CRN list does not establish that the ingredient was marketed prior to the enactment of DSHEA:

Although reference to a publication listing a substance chemically identical to [a dietary ingredient] as having been marketed prior to October 15, 1994, might buttress a claim that [the ingredient] is not a new dietary ingredient, the inclusion of such a substance in one or more of these published lists does not, by itself, suffice to show that the substance is not a new dietary ingredient. You also need to demonstrate that the listing of a substance chemically identical to [the ingredient] as an "old" dietary ingredient in the publication or publications at issue is founded on accurate and reliable evidence sufficient to support a finding that [it] was marketed as a dietary ingredient prior to October 15, 1994. In the alternative, you could submit independent documentation that [it] is not a new dietary ingredient, such as an invoice, a bill of lading, or a product label establishing that a substance chemically identical to [the ingredient] was marketed as a dietary ingredient prior to October 15, 1994.

Letter from FDA to Holly M. Bayne (July 15, 2001) ("Bayne Letter") (attached at Tab 7).

Because there is no evidence that it was marketed in the United States before October 15, 1994, P5P qualifies as a new dietary ingredient. Therefore, any dietary supplement containing P5P must either: (1) contain only dietary ingredients (including P5P) 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; or (2) be the subject of a 75-day pre-market notification providing a basis for concluding that the ingredient is safe when used under the conditions recommended or suggested in the product's labeling.

2. P5P Has Not Been Present In The Food Supply As An Article Used For Food And No 75-Day Pre-Market Notification Has Been Submitted To FDA.

P5P has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered, and Medicare is unaware of any 75-day pre-market notification having been submitted to FDA. *See* 21 U.S.C § 350b(a). Accordingly, all dietary supplements containing P5P are adulterated under the FDCA. *See* 21 U.S.C. §§ 331(a), 331(v), 342(f).

As noted above, P5P is the phosphorylated form of pyridoxal, a coenzyme belonging to the vitamin B6 family. Pyridoxal, in turn, is derived through the oxidation of pyridoxine or pyridoxamine, two other forms of vitamin B6. P5P is present in the muscle protein of animal products; importantly, however, this minimal presence is not sufficient to exempt P5P from the pre-market notification process.

FDA takes the position that the “mere incidental presence of a substance as an inherent component of articles used for food does not establish that the substance itself is ‘an article used for food.’” Bayne Letter (emphasis added); *see* Letter from FDA to Beth Thompson (Apr. 2, 2003) (attached at Tab 8) (“The mere incidental presence of components of [an ingredient] or [the ingredient] itself as inherent components of articles used for food does not establish that section 350b(a)(1) applies.”) (emphasis added). Thus, the minor amounts of P5P that happen to be present in the food supply in meat and other animal products – an incidental by-product of those animals’ consumption and metabolism of vitamin B6 – do not qualify P5P as being held as an “article used for food.”

Furthermore, Medicare believes that no company marketing a dietary supplement containing P5P has made a 75-day pre-market notification to FDA. To determine whether such a notification has been made, Medicare and outside consultants conducted several searches of FDA’s website and commercially available databases of dietary supplement notifications. We found no indication that a 75-day notice had been filed for any dietary supplement containing P5P.

Accordingly, P5P-containing dietary supplements currently marketed in the United States are adulterated and their distribution is prohibited by the FDCA. For this reason, FDA should take action against any company that is marketing a dietary supplement containing P5P. This is consistent with the agency’s announced enforcement priorities.⁶ Moreover, in addition to the safety concerns that the 75-day notification procedure is attended to address, the impact on Medicare’s ability to develop P5P as a new drug for the treatment of unmet medical needs requires immediate action by the agency.

**C. Dietary Supplements Containing P5P Violate The “Exclusionary Clause”
And Should Immediately Be Removed From the Market.**

DSHEA’s definition of “dietary supplement” includes two provisions intended to protect the incentives of pharmaceutical companies to develop innovative drugs, by prohibiting the marketing of dietary supplements containing the ingredients under development. One of these, known as the “exclusionary clause,” specifically excludes from the definition of dietary supplement, among other things, an article that is authorized for investigation as a drug, for which substantial clinical

⁶ According to a recent speech by the Director of FDA’s Center for Food Safety and Applied Nutrition, dietary supplements containing new dietary ingredients that are sold without submission of the 75-day pre-market notice are among the Center’s top enforcement priorities. *See Un-Notified NDIs Concern FDA; CFSAN Looks At Enforcement Options*, FDC Reports (Oct. 9, 2007) (attached at Tab 9).

investigations have been instituted and for which the existence of such investigations has been made public, unless the article was marketed as a dietary supplement or as a food before the investigation was authorized. *See* 21 U.S.C. § 321(ff)(3)(B).

FDA has summarized the purpose of this provision as follows:

Stated simply, the statute prohibits the marketing as dietary supplements of articles that have gained recognition in the marketplace as new drugs by either being approved or studied as new drugs. DHSEA reflects Congress's determination that to allow such an article to be marketed as a dietary supplement would not be fair to the pharmaceutical company that brought, or intends to bring, the drug to market, and would serve as a disincentive to the often significant investment needed to gain FDA approval of new drugs.

Pharmanex, Inc., Administrative Proceeding, Docket No. 97P-0441; Final Decision (May 20, 1998) (attached at Tab 10).

Thus, where an ingredient is being studied as a drug and where the existence of substantial clinical investigations has been made public, that ingredient may be marketed in a dietary supplement only if the ingredient was marketed prior to the date the drug was authorized for investigations (*i.e.*, prior to the date an IND went into effect). Permitting an ingredient to be marketed as a dietary supplement, despite clinical investigations that pre-date such use, would, as FDA has recognized, be fundamentally unfair to the pharmaceutical company sponsoring the investigations and would undermine the incentive for all pharmaceutical companies to develop such drugs.

As noted above, Medicure's IND for P5P was submitted to FDA on November 23, 2001. It was received by FDA on November 26, 2001, and went into effect 30 days thereafter. Substantial clinical investigations of the drug were begun, and their existence has been widely publicized. In light of Medicure's significant investment in developing P5P as a new drug for the treatment of ischemia and/or ischemia reperfusion injury, dietary supplements containing P5P may not be marketed unless they were lawfully marketed before Medicure's IND went into effect.

Medicure is aware that dietary supplements containing P5P were marketed prior to December 2001. As discussed above, however, none of these products was lawfully marketed because P5P is a new dietary ingredient for which no 75-day pre-market notification has been submitted. In interpreting the exclusionary clause, the term "marketed" must be read to mean "lawfully marketed." While the clause itself is silent on the issue, it would be absurd for Congress to have enacted a provision that would allow a dietary supplement company to eviscerate the incentive for drug development by unlawfully marketing a product.⁷ Unless the clause is interpreted to require lawful marketing, it will

⁷ It is a fundamental tenet of statutory construction that a statute must be interpreted to avoid such absurd results, in conflict with the overall goal of the statutory regime. *See, e.g., Shapiro v. United States*, 335 U.S. 1, 31 (1948); *U.S. v. American Trucking Ass'ns*, 310 U.S. 534, 543 (1940); *Armstrong Paint & Varnish Works v. Nu-Enamel Corp.*, 305 U.S. 314,

create an incentive for companies to market supplements unlawfully; surely this cannot have been Congress's intent.

The continued marketing of P5P-containing dietary supplements therefore violates DSHEA's exclusionary clause, and does precisely what the clause was enacted to prevent – threatens Medicare's development of MC-1, and rewards dietary supplement companies that have thwarted clear statutory and regulatory requirements. If such unlawful products are permitted to remain on the market, pharmaceutical companies will have significantly less incentive to pursue costly and time-consuming clinical investigations. For these reasons, FDA should take immediate action to remove these products from the marketplace.⁸

D. If FDA Declines To Take Immediate Action, It Should Begin A Rulemaking To Exclude P5P-Containing Dietary Supplements From The Market.

Even if an ingredient were lawfully marketed as a dietary supplement before it was investigated as a drug (which is not the case here), FDA has ample authority to issue a regulation prohibiting the sale of such ingredient in a dietary supplement. For example, DSHEA grants FDA specific authority to issue a regulation excluding from the definition of a dietary supplement an article that is approved as a drug and was, prior to such approval, marketed as a supplement. *See* 21 U.S.C. § 321(ff)(3)(A). This is in addition to the agency's general rulemaking authority. *See* 21 U.S.C. § 371(a). These present means by which FDA can protect the incentives for drug development, and allow the agency to balance, on a case-by-case basis if necessary, the competing interests of dietary supplement and pharmaceutical companies.

To be sure, lawfully marketed dietary supplements should not be removed from the market simply because science advances to a point where the safety and effectiveness of a dietary ingredient in treating a disease are recognized. On the other hand, pharmaceutical companies developing new drugs must be protected from companies that may seek to market the ingredients in those drugs as dietary supplements. The marketing of such products has the potential to undermine the incentives for the development of new drugs, because many people may choose to purchase the supplements rather than the drugs. This may also endanger the health of those who purchase the supplements, instead of taking the drug products under the supervision of their physicians. FDA's rulemaking authority provides a means for interested parties and the public to comment on those competing interests in a specific situation, and for the agency to evaluate the relevant factors and make a considered decision.

333 (1938) (describing the canon of construction that statutes should be interpreted to avoid absurd results, or those plainly at variance with the policy of the legislation as a whole).

⁸ *See Pharmedex v. Shalala*, 221 F.3d 1151, 1159 (10th Cir. 2000) (applying the exclusionary clause, and stating that “[t]o permit manufacturers to market dietary supplements with components identical to the active ingredients in prescription drugs would, as the FDA points out, contravene the incentive structures in place in the FDA for the development of orphan drugs and pediatric drugs”).

Medicure has invested over \$60 million in the development of P5P as a novel cardioprotective agent for the treatment of cardiovascular events associated with ischemia and/or ischemia reperfusion injury. The company has completed many Phase I and II clinical trials, and has recently completed enrollment in a large, Phase III trial. Medicure's product, MC-1, has Fast Track designation from FDA, reflecting the drug's potential to address unmet medical needs in the treatment of a life-threatening disease. The continued marketing of P5P-containing dietary supplements may detrimentally affect the market for the drug product under development. Moreover, the mere potential for this to occur could undermine the company's market value, its capacity to raise capital, and therefore its ability to continue with its development plans. It is particularly egregious that this is being done by dietary supplements that are adulterated. To protect the incentive for Medicure, and other companies, to develop innovative drugs for the treatment of life-threatening diseases, and to further the policy goals of DSHEA's exclusionary clause, FDA should issue a regulation prohibiting the marketing of P5P as a dietary ingredient.

III. Environmental Impact

This citizen petition qualifies for a categorical exclusion under 21 C.F.R. § 25.30.

IV. Economic Impact

Information on economic impact will be provided upon request by the Commissioner.

V. Certification

I certify that, to the best of my knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted during the clinical development of P5P. I do not expect to receive payments, including cash and other forms of consideration, to file this information or its contents. I verify under penalty of perjury that the foregoing is true and correct as of the date of this submission of this petition.

Respectfully submitted,



Albert D. Friesen, Ph.D.
President and Chief Executive Officer
Medicure Pharma