Case #5333 (05/12/11)
NEW NORDIC US INC.
Mulberry Zuccarin Dietary Supplement
Challenger: National Advertising Division

- **Health related advertising claims must typically be supported by competent and reliable scientific evidence in the form of well-controlled studies, the results of which should translate into a meaningful benefit for consumers and relate directly to the performance promised in the advertising.**

- **The nature and extent of claims made by an advertiser should mirror/be directly analogous to the precision and specificity of the data used to substantiate them.**

- **In addition, clinical studies offered to support product performance claims should, as a general rule, follow the product's use instructions.**

Basis of Inquiry: As a part of its ongoing monitoring program and in conjunction with NAD's initiative with the Council for Responsible Nutrition ("CRN") designed to expand NAD's review of advertising claims for dietary supplements, NAD inquired about certain advertisements disseminated by New Nordic US Inc. ("New Nordic") for its Mulberry Zuccarin ("Zuccarin") dietary supplement product. The advertising, which appeared in print, on product labeling, and on the Internet, included the following claims:

"In the small town of Alesund in Norway, people have been introduced to a secret about weight loss that made over 1500 of them lose weight."

"I went down 6 clothing sizes! … My health food store owner, Johnny, recommended Mulberry Zuccarrin. Very quickly, I felt a decrease in my sugar cravings and an increase of energy. … I tell my friends who want to lose weight to take Mulberry Zuccarin."

"Stabilize your blood sugar levels with this new highly concentrated mulberry leaf extract."

"Block carbohydrate digestion and regulate your blood sugar with this new unique and highly concentrated mulberry leaf extract."

"Mulberry Zuccarin is a natural product, which helps maintain healthy blood sugar levels."

Advertiser's Position:

As a preliminary matter, the advertiser provided the NAD with information regarding the ingredients comprising Zuccarin as well as the health benefits of these ingredients. Specifically, the advertiser noted that Zuccarin contains a single botanical dietary ingredient, White Mulberry (Morus alba L.) Extract, which is derived from ground Mulberry leaf and is offered in a tablet dosage of 400 mg per serving. According to the advertiser, each tablet dosage contains 1% (4mg) of the bioactive constituent 1-deoxynojirimycin (DNJ), a naturally occurring glucose analogue with a secondary amine group instead of an oxygen atom in the pyranose ring of

glucose. The advertiser noted that label recommendations on the product advise consumers to take one to three tablets (400 – 1200 mg) per day.

The advertiser asserted that DNJ is the most bioactive and abundant of the iminosugars contained in Mulberry leaf and is considered an alpha-glucosidase inhibitor, specifically, a competitive inhibitor of small-intestinal brush-border α-glucosidase. The advertiser also noted that DNJ is used as a prescription drug in Europe for the control of obesity.

I. Zuccarin Helped 1,500 Subjects Lose Weight

The advertiser relied on the testimony of Johnny Pettersen, the individual featured in the advertisement, to support the claim that "1500 customers lost weight" using Mulberry Zuccarin. The advertiser stated that, although this claim is true, it was not able to obtain a sufficiently validated quantitative assessment establishing subject weight loss and therefore conceded that this claim is not supported by the level of scientific evidence consistent with other allowable claims reviewed in previous NAD decisions.

The advertiser agreed to discontinue its use of the claim "Zuccarin helped 1500 subjects lose weight" until the statement can be quantified in a controlled setting in Alesund, Norway, which allows for cause and effect to be established.

II. Zuccarin Blocks Carbohydrate Digestion

The advertiser explained that alpha-glucosidase is a key enzyme necessary to metabolize non-absorbable oligosaccharides into absorbable monosaccharides in the small intestine. The advertiser went on to explain that alpha-glucosidase inhibitors, such as Acarbose, Miglitol and Voglibose, are oral anti-diabetic drugs used in the control of blood sugar disorders such as diabetes mellitus. These drugs work by inhibiting the enzymes needed to digest carbohydrates, either in the pancreas or at the brush-border membrane of the small intestine. According to the advertiser, DNJ (the bioactive compound found in mulberry leaves) is also identified as a potent alpha-glucosidase inhibitor at the brush-border membrane of the small intestine as well as alpha-amylase – the two enzymes required for carbohydrate digestion.[1] The advertiser maintained that there is no debate on the status of DNJ as an alpha-glucosidase inhibitor, or its ability to inhibit other enzymes responsible for glucose or polysaccharide absorption. In particular, the advertiser stated that inhibition of such enzymes decreases the rate of digestion of carbohydrates, preventing the breakdown to absorbable glucose molecules. The effect serves to decrease blood glucose levels and reduce hemoglobin A1c levels.[2]

The advertiser submitted Park et al., 2009, as evidence to support the claim that this ingredient blocks carbohydrate absorption. According to the advertiser, the Mulberry leaf powder administered in this study reduced peak responses of blood glucose significantly in both non-

[1] Yoshihashi, 2010; Zechel, 2003; Ermert, 1991.
[2] Kojima, 2010.

obese (Goto-Kakizaki) rats and obese (Wistar) rats, supporting the inhibition of alpha-glucosidase by Mulberry in the small intestine.[3]

In addition, the advertiser noted that in the study by Oku, 2006, sections of human and rat small intestine were used to confirm the inhibitory action of DNJ. In both samples, sucrase, maltase and isomaltase, were conspicuously and completely inhibited, demonstrating that digestion of sucrose or polysaccharide is suppressed when an appropriate amount of Morus alba is orally ingested. The advertiser emphasized that the Mulberry used here at 0.24% is roughly equivalent (6 mg) to that used in Mulberry Zuccarin (4 mg) (on an equivalent basis), adding that the results of this study showed a linear progression of dosage to inhibitory activity.[4]

These results, according to the advertiser, are consistent with the in-vivo study conducted by Miyahara et al., that showed treatment of rats with Mulberry extract significantly suppressed plasma glucose levels after loading with sucrose, maltose or starch, with the most potent suppressive effect observed with sucrose. The advertiser further noted that this study also demonstrated a potent suppressive effect of Mulberry extract on sucrose (among 4 types of disaccharidase in the small intestine), demonstrating a suppressive effect of blood glucose uptake in the small intestine.[5]

In the study by Mudra et al., ten healthy control subjects and ten type II diabetic patients received a Mulberry leaf extract (1 gram, equivalent to 3-5 mg total DNJ content) with 75 g sucrose. Compared to placebo, co-ingestion of Mulberry produced significant reductions in blood glucose, and the H2 concentrations were greater ($p<0.01$) in the Mulberry vs placebo treatment for both groups, indicating significant mal-absorption of sucrose.[6]

Finally, in the study by Zhong et al., 2006, 20 subjects ages 23-60 were provided a Mulberry, green and black tea capsule (equivalent to 5 mg total of DNJ). The investigators studied the ability of each to interfere with carbohydrate and triacylglycerol absorption via their ability to inhibit alpha-amylase, alpha-glucosidase, sodium-glucose transporters and pancreatic lipase. Breath hydrogen and CO2 output were used as measurements. Results demonstrated a highly significant increase in breath-hydrogen concentrations, indicating appreciable carbohydrate mal-absorption.

III. Zuccarin Stabilizes Blood Sugar, Regulates Blood Sugar, and Helps Maintain Healthy Blood Sugar

The advertiser maintained that its claims that Mulberry Zuccarin stablizes blood sugar, regulates blood sugar, and helps to maintain healthy blood sugar are supported by sufficient scientific evidence. As a preliminary matter, the advertiser noted that New Nordic Mulberry Zuccarin has

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[3] Park, 2009
[4] Oku, 2006.
[5] The advertiser stated that the dosage equivalence is 6-24 mg DNJ (0.1-0.4 g/kg = 6-24g of EM/60kg human or 6-24 mg of DNJ/60 kg human) (Miyahara, 2004).
[6] Mudra, 2007.

received approval from Health Canada for sale of this product with the claim "Helps to Promote healthy glucose levels."

According to the advertiser, both the clinical and preclinical scientific support submitted offer clearly defined effects on fasting and post-prandial blood glucose levels at the dosage levels advocated by New Nordic in Zuccarin Mulberry.

In particular, the advertiser stated that, in the study by Park et al., 2009, Mulberry leaf powder administered to both non-obese (Goto-Kakizaki) rats and obese rats (Wistar) significantly reduced fasting blood glucose at weeks 4 and 5 ($P<0.05$). In addition, the advertiser stated that in the study by Kong et al., 2008, DNJ treatment showed significant anti-diabetic effects in OLETF (diabetic) rats, with significant improvements in fasting blood glucose levels and glucose tolerance. Here, daily treatment with 100 mg/kg DNJ in OLETF (diabetic) and LETO (non-diabetic) rats resulted in significant improvements in blood glucose tolerance. The advertiser emphasized that, in this study, DNJ lowered blood glucose concentrations from 3 to 60 minutes after glucose stimulation ($P<0.01$), adding that this model also demonstrated significant suppression of weight gain in diabetic rats without adjustments to food intake.

Next, the advertiser noted that in the study by Naowaboot, 2009, male Sprague-Dawley rats (200-250g) given a Mulberry leaf extract (yield 23.70% of dry leaves) were used to evaluate the effect on blood glucose, oxidative damage and glycation. Here, daily administration of 1 g/kg Mulberry leaf extract for six weeks decreased blood glucose by 22% ($P<0.05$). Hemoglobin A1c (a biomarker for chronic exposure to high concentration of glucose) was also significantly decreased in the Mulberry treated group in comparison to the untreated group. Antiglycation effects were also significant.

The advertiser also referred to the study by Kimura et al., where the effects of a DNJ rich Mulberry leaf extract upon the suppression of abnormally high blood glucose levels were analyzed. Here, twenty four healthy volunteers received 0, 0.4, 0.8 and 1.2 grams of DNJ enriched powder (corresponding to1, 6, 12 and 18 mg of DNJ, respectively), followed by 50 grams of sucrose. The results demonstrated that both dosages of 12 mg and 18 mg DNJ significantly suppressed the elevation of postprandial blood glucose and secretion of insulin, revealing the physiological impact of Mulberry DNJ (effective dose and efficacy in humans). Kimura et al., concluded that the DNJ-enriched powder can inhibit all or some intestinal disaccharidases, which regulate the absorption of carbohydrates, making DNJ a feasible oral treatment of NIDDM. The advertiser emphasized that Kimura later reconfirmed the effectiveness of the dosage of DNJ at 12 mg, where a DNJ rich Mulberry leaf powder (1.5% DNJ equivalent to 12 mg DNJ) was evaluated over a 38 day period. These results demonstrated statistically significant suppression of postprandial blood glucose and secretion of insulin in human subjects.[7]

The advertiser also referred to a study by Andallu et al., which compared the effects of Mulberry leaf extract with glibenclamide. Here, Mulberry therapy significantly reduced fasting blood

[7] Kimura, 2010.

glucose concentrations of twenty four diabetic individuals, leading the authors to conclude that Mulberry therapy exhibits potential hypoglycemic and hypolipidemic effects in diabetic patients.[8]

Finally, the advertiser stated that in the study by Mudra et al., ten healthy control subjects and ten type II diabetic patients received a Mulberry leaf extract (NatureGen mulberry 1 gram, containing an estimated 3-5 mg DNJ) with 75 g sucrose. Here, blood glucose was assessed before and at intervals over 120 min after sucrose ingestion and 180-240 min in type II diabetic subjects. Compared to placebo, co-ingestion of mulberry produced significant reductions in blood glucose.

Decision:

As a preliminary matter, because of the nature of this product, and the types of potential consumers that would purchase it (i.e., diabetics or those with blood sugar issues and potentially undiagnosed diabetes) NAD recommended that the advertiser include a prominent disclosure in all advertising for Mulberry Zuccarin, advising consumers that "Mulberry Zuccarin is not a prescription drug," and is "not intended to replace medications."

I. *Testing*

The advertiser did not conduct any testing on the Mulberry Zuccarin product itself. In place of product testing the advertiser relied on studies conducted on the product's active ingredient, the bioactive constituent 1-deoxynojirimycin ("DNJ").

The advertiser's primary evidence was the Kimura 2007 study, a human study conducted on twenty four healthy volunteers divided into 4 groups of 6 individuals. Each group received 0 (placebo), 0.4, 0.8, or 1.2 g of DNJ-enriched powder (corresponding to 0, 6, 12, or 18 mg of DNJ, respectively), followed by 50 g of sucrose dissolved in 100 mL of water. Blood samples were collected before DNJ/sucrose intake and 30, 60, 90, 120, 150 and 180 minutes after the administration. According to the study, the single oral administration of 0.8 and 1.2 g of DNJ-enriched powder (corresponding to 12 mg and 18 mg of DNJ) significantly suppressed the elevation of postprandial blood glucose and secretion of insulin.

In addition to Kimura et al., the advertiser referred to four additional human clinical studies on Mulberry: Mudra et al., 2007; Zohng et al., 2006; and Andallu et al., 2001. The advertiser's remaining evidence consisted of studies conducted on rats.

In Mudra et al., ten healthy control subjects and ten type II diabetic subjects (without complications) were randomly assigned to receive either placebo or 1 g of Mulberry leaf extract (the study did not indicate the level of DNJ present in the extract) with 75 g sucrose in 500 mL

[8] The advertiser noted that the dosage of 3 grams mulberry, at the estimated level established at 0.1% DNJ = 3 mg DNJ for the intervention.

hot water. The results demonstrated that, compared with placebo, co-ingestion of Mulberry produced a significant reduction in blood glucose increases for the initial 120 minutes of testing in both control and type II diabetic subjects.

Zohng et al., used a crossover design in which twenty healthy volunteers (ten women and ten men) randomly ingested test meals with either a placebo beverage or a preparation containing Black (0.1 g), Green (o.1 g), and Mulberry (1.0g) teas. The study reported that when the tea was consumed with the meal participants showed a highly significant increase in breath-hydrogen concentrations, which indicated appreciable carbohydrate malabsorption.

Finally, Andallu et al., was designed to investigate the effect of Mulberry leaves on plasma and erythrocyte membrane lipids in type II diabetic patients. In addition, the anti-diabetic activity of Mulberry therapy was compared with the standard drug, glibenclamide, routinely used for hyperglycemic control in diabetic patients. In this study, twenty-four male mild type II diabetic patients with no other severe complications were recruited from the diabetic out patient clinic of K.M. Hospital for diabetes, Anantapur, Andhra Pradesh, India. Patients were randomly divided into two equal groups, each group was treated with either Mulberry or glibenclamide. In this study, fresh young Mulberry leaves were collected from the Regional Sericultural Research Station, Anantapur, Andhra Pradesh, India. The leaves were washed thoroughly under running water to remove the adhering foreign particles and pesticides. The leaves were then shade-dried, powdered and filled into capsules. The subjects designated for Mulberry therapy were given six capsules of Mulberry leaf powder three times a day, i.e., two after every meal, which amounts to a dose of 3 g Mulberry powder per day. Patients designated for standard drug therapy were given one tablet of glibenclamide per day. There was no reference to how much DNJ each capsule contained. Andallu et al., concluded that this testing provides preliminary data suggesting that Mulberry therapy is capable of enhancing glycemic control in patients with type II diabetes. The study noted, however, that much work must still be performed to verify these results and define the precise mechanisms involved in improving the glycemic control by Mulberry therapy. The study further noted that additional verification of these results in a long-term clinical trial is necessary to understand the long-term effects of Mulberry therapy in controlling diabetes.

II. *Weight Loss Claims and Consumer Testimonials*

As noted in the advertiser's position above, the advertiser relied on the testimony of Johnny Pettersen (the individual featured in the advertisement) to support the claim that "1500 customers lost weight" using Mulberry Zuccarin. The advertiser conceded that it does not have scientific evidence to support this statement, and therefore, agreed to discontinue the claim, an action NAD deemed both necessary and appropriate.

In addition to the claim "1500 customers lost weight" the challenged advertisement makes several other references to Mulberry Zuccarin's ability to generate weight loss. The advertisement also features a consumer testimonial from a woman named "Heidi" from Alesund, Norway, which states:

> "I used to weigh 188lbs, a few years ago, which is about 45 lbs overweight for my size. After making changes to my diet, I managed to lose a few pounds, but never reaching my ideal weight. I felt that the scale was standing still for me. My health food store owner, Johnny, recommended Mulberry Zuccarin. Very quickly, I felt a decrease in my sugar cravings and an increase of energy. I went down 6 clothing sizes and my weight is now stable at 141 lbs. I tell all my friends who want to lose weight to take Mulberry Zuccarin."

It is well-established that testimonials and anecdotal evidence are insufficient substantiation for performance claims for dietary supplements and health-related products.[9] The evidence submitted by the advertiser focused on blocking carbohydrate digestion and lowering blood sugar levels, which may, *indirectly* lead to weight loss. However, none of the evidence in the record measured weight loss, let alone the rather drastic weight loss claimed in this testimonial (6 clothing sizes or approximately 47 lbs). For these reasons NAD recommended that the advertiser discontinue *all* weight loss claims including the testimonial by "Heidi".

III. *"Stabilize your blood sugar levels with this new highly concentrated mulberry leaf extract." "Block carbohydrate digestion and regulate your blood sugar with this new unique and highly concentrated mulberry leaf extract." "Mulberry Zuccarin is a natural product, which helps maintain healthy blood sugar levels."*

Health related advertising claims must typically be supported by competent and reliable scientific evidence in the form of well-controlled studies, the results of which should translate into a meaningful benefit for consumers and relate directly to the performance promised in the advertising. It is well-established NAD precedent that the nature and extent of claims made by an advertiser should mirror, or be directly analogous to, the precision and specificity of the data used to substantiate them. In addition, NAD emphasized that clinical studies offered to support product performance claims should, as a general rule, follow the product's use instructions.

The product use instructions for New Nordic Mulberry Zuccarin state that one tablet should be taken before each meal, up to three times daily. As the advertiser explained in its submission, each 400 mg one-dosage tablet of Mulberry Zuccarin is standardized to contain 1% (or 4 mg) of the bioactive constituent 1-deoxynojirimycin ("DNJ"). Thus, consumers following the product use instructions would receive 4 mg DNJ before each meal.

The advertiser's primary evidence submitted to support its claims that Mulberry Zuccarin stabilizes blood sugar levels and blocks carbohydrate digestion, Kimura et al., demonstrated that the effective dose of DNJ was 12 mg. The remaining clinical studies submitted to support these claims either did not state the exact amount of DNJ present in the Mulberry extract tested (Mudra), did not test Mulberry in the same form as the Mulberry Zuccarin product (Zhong tested a preparation of black, green and mulberry tea), or, tested Mulberry in a different form *and* did not provide the level of DNJ tested (the Andallu study tested the application of dried and

[9] Sunset Int. distribution, LLC and Rozge' Cosmeceutical (NewCurves Breast Enhancements Formula), Case # 4033,*NAD/CARU Case Reports* (April 2003).

powdered Mulberry leaves and did not indicate the level of DNJ present). In addition, NAD noted the relatively small study populations (i.e., twenty-four volunteers in Kimura et al.,) in contrast with the strong claims being made.

Although the advertiser submitted over 23 studies (many conducted on rats) on the effects of Mulberry extract or DNJ, not one of the studies demonstrated that 4 mg of DNJ, taken before a meal, would block carbohydrate digestion or regulate blood sugar levels. For these reasons, NAD determined that the advertiser's evidence is not sufficient to support the rather strong product performance claims that Mulberry Zuccarin "blocks carbohydrate digestion" or "stabilizes blood sugar levels" and, consequently, recommended that both claims be discontinued.

In contrast, NAD concluded that the advertiser's evidence is sufficient to support more mild claims like "Mulberry Zuccarin is a natural product which *helps maintain* healthy blood sugar levels already within normal levels" (emphasis added) when 12 mg DNJ are taken before each meal (as the advertiser's evidence demonstrates). For these reasons, NAD recommended that the advertiser either change its product use instructions, and recommend 3 tablets (12 mg DNJ) before each meal, to match the amount used in the advertiser's primary scientific support (Kimura, 2007), or, discontinue the use of such claims.

Conclusion:

As a preliminary matter, because of the nature of this product, and the types of potential consumers that would purchase it (i.e., diabetics or those with blood sugar issues and potentially undiagnosed diabetes) NAD recommended that the advertiser include a prominent disclosure in all advertising for Mulberry Zuccarin, advising consumers that "Mulberry Zuccarin is not a prescription drug," and is "not intended to replace medications."

The advertiser agreed to discontinue the claim, "1500 customers lost weight", an action NAD deemed both necessary and appropriate.

NAD determined that the evidence in the record is insufficient to support weight loss claims, including the consumer testimonial by "Heidi" as well as claims that the product blocks carbohydrate digestion or stabilizes blood sugar levels, and consequently, recommended that these claims be discontinued.

NAD determined that the advertiser's evidence is not sufficient to support the rather strong product performance claims that Mulberry Zuccarin "blocks carbohydrate digestion" or "stabilizes blood sugar levels" and, consequently, recommended that both claims be discontinued.

Finally, NAD determined that the advertiser has sufficient evidence to support the claim that "Mulberry Zuccarin is a natural product, which helps maintain healthy blood sugar levels already within normal levels", when 12 mg DNJ are taken before each meal. Therefore, NAD

recommended that the advertiser either change its product use instructions, and recommend 3 tablets (12 mg DNJ) before each meal, to match the amount used in the primary study (Kimura, 2007), or discontinue the claim.

Advertiser's Statement:

New Nordic will discontinue the advertising in question. In addition, New Nordic agreed to include the following disclaimer in future advertising: "Mulberry Zuccarin is not a prescription drug and is not intended to replace medications." **(#5333 KLF, closed 05/12/2011)**