CHRISTOPHER
&
WEISBERG, P.A.
ATTORNEYS AT LAW

June 10, 2002

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements
(HFS-820)
Center For Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: Pre-Market Notification Letter Pursuant to 21 CFR § 190.6

Dear Sir or Madam:

Pursuant to 21 U.S.C. 350b, "New Dietary Ingredients," and Food and Drug Administration (FDA) regulations, 21 C.F.R. 190.6, "Requirement for Pre-Market Notification," I hereby submit on behalf of my client, Natural ASA, located at Kjorbokollen 30 N-1337 Sandvika, NORWAY, this new dietary ingredient (NDI) notification to the FDA for conjugated linoleic acid (CLA) to be manufactured and/or distributed by Natural ASA under the trademark Tonalin.

Natural ASA (or its affiliates) has been marketing CLA products in the United States since 1998. At the time of introduction of Natural's CLA products into the United States market in 1998, no NDI pre-market notification letter had been submitted to FDA. No NDI pre-market notification letter was submitted because at that time Natural ASA formed the opinion that the CLA contained in its products was not an NDI as defined by 350b.

As CLA is a naturally occurring ingredient, which is available in red meats and milks, it was concluded that since the CLA available in meats and milks was available in

200 EAST LAS OLAS BOULEVARD, SUITE 2040 FORT LAUDERDALE, FLORIDA 33301
TELEPHONE (954) 828-1488 FACSIMILE (954) 828-9122
www.cwcip.com

the food supply chain prior to the enactment of the Dietary Health and Education Act (DSHEA) in 1994, that the chemically equivalent CLA in Natural ASA's products was also available in the food supply chain prior to 1994, and therefore an NDI pre-market notification letter was not required.

Natural ASA still holds the opinion that since CLA was available in the food supply chain prior to 1994 in meats and milks, that the CLA in its products is not an NDI.

However, the CLA products marketed by Natural ASA contain CLA that is isolated and purified from safflower oil. As such, Natural ASA's CLA products contain higher concentrations of CLA than are found in meats and milks. One could suggest that the higher concentrations present in Natural ASA's CLA products warrants an NDI notification.

Accordingly, Natural ASA is now submitting this NDI market notification letter as a prophylactic measure and to be in full compliance with the regulations in view of possible differing opinions as to the status of CLA as an NDI. This notification is intended to inform FDA of Natural ASA's (including affiliates and licensees) current marketing of the products listed herein, and its intent to further market the same and similar products.

I. Name of the New Dietary Ingredient

A. Free Fatty Acid Product

Conjugated Linoleic Acid (CLA) (geometric isomers of Octadecadienoic Acid) Formulated as free fatty acid (FFA) products (technical data and specification attached as Exhibit A); and

B. Triglyceride Product

Conjugated Linoleic Acid (CLA) (geometric isomers of Octadecadienoic Acid) Formulated as triglyceride (TG) products (technical data attached as Exhibit B).

II. Description of the Dietary Supplements

A. Level of the New Dietary Ingredient

750 milligrams per capsule composed of various mixtures of different isomers of CLA, see Exhibit A

B. Conditions of Use

Up to a maximum daily dosage of 3.4 grams or 6 capsules.
Two capsules to be taken 3 times daily with meals.

III. Evidence of Safety

Natural ASA introduced its CLA product into the European market as a dietary ingredient for body fat reduction in 1996. The first year's sales amounted to approximately 30,000 boxes (One box containing 100 capsules x 750 mg). Since then the yearly sales in the Nordic area have increased to a maximum of 54 tons in year 2000, (equivalent to 720,000 boxes). A total of 130 tons (1.7 million boxes) have been sold throughout the world.

Sales of Tonalin CLA into the North American market started in 1998 and reached a peak of 126 tons in 2001. During the first quarter of 2002 the total sales in the region amounted to 303 tons (more than 4 million boxes). In the same period the total figure for the Nordic area was 127 tons, or 1.7 million boxes.

The recommended condition for use of the preparation includes dietary regimens aiming at body fat loss without loss of muscle mass, and the suggested daily dosage in adults is 3.4 .g / day or 6 capsules per day. As such, the total Tonalin CLA sales in 2001 amounting to 176 tons or 2.35 million boxes (39 million daily doses in 2001).

Natural ASA continuously monitors adverse event occurrences. However, registration of adverse events by so-called spontaneous reporting is less satisfactory than direct registration from clinical trials. Therefore such trials with a proper registration of adverse events have been performed, and four of them will be discussed herein.

Further, Natural is currently conducting a major long-term trial with Tonalin CLA, which is currently in its final phase.

A. <u>Clinical evidence of safety:</u>

Attached please find the scientific studies, which establish that this dietary ingredient, when used under the conditions suggested in the labeling of the dietary supplement, is reasonably expected to be safe. This information includes:

Exhibit C: Summary of Articles submitted

Exhibit D: *Safety of conjugated linoleic acid (CLA) in overweight or obese human volunteers*, Berven et al. (2000)

Exhibit E: *Congugated Linoleic Acid Reduces Body Fat Mass in Overweight and Obese Humans*, Blankson et al. (2000)

Exhibit F: *Conjugated Linoleic Acid Supplementation in Humans-Metabolic Effects*, Smeedman & Vessby (2001)

Exhibit G: *Conjugated linoleic acid (CLA) reduced abdominal adipose tissue in obese middle-aged men with signs of the metabolic syndrome: a randomized controlled trial*, Riserus et al. (2001)

B. Review of Clinical Studies:

i. Short term studies:

CLA, being a nutritional substitution, has mainly been given to obese and moderately overweight healthy volunteers in the studies performed up to date. In the Norwegian study, Berven et al (2000) (Attached as Exhibit D), the primary aim was to evaluate safety of CLA, while investigating the effect on body composition. The study was double-blind and randomised. A daily dosage of 3.4 grams of CLA was compared to placebo (olive oil) in 60 overweight or obese subjects for a period of 12 weeks. Three adverse events were recorded in the CLA group:

Two cases of loose stool, and one case claiming *foetor ex ore* and bad perspiration smell; while three events occurred in the placebo group: loose stools, heartburn and haemorrhagic gastritis. All cases were considered mildly to moderately severe, and treatment was continued except for the placebo case with GI-bleeding and the verum case with bad oral smell; here both subjects chose
to leave the study. As to blood parameters measured at baseline and week 12 there were no changes indicating harmful effects of the treatments given.

Another Norwegian study, Blankson et al (2000) (Attached as Exhibit E), investigated the effect of CLA given for 12 months on body fat mass in 60 overweight or obese individuals. In this placebo-controlled, dose-response study, CLA dose ranged from 1.7 to 6.8 grams per day. No statistically significant differences as to the occurrence of adverse events were observed between the groups. The majority of untoward reactions were of gastrointestinal origin and could be supplement related; the severity of which were mild-to-moderate. One event was classified as serious (relapse of asthma, daily dose 3.4 g CLA/day) , but judged to be unrelated to study supplement.

Results in a third study, Smedman & Vessby 1999 (Attached as Exhibit F), confirm the safety profile shown in the two studies described above. Here 53 healthy subjects were randomly assigned to either CLA 4.2 g / day or control capsules containing olive oil for a period of 12 weeks. All participants completed the trial, and the capsules were well tolerated, and only a few subjects reported mild diarrhoea at some occasions. No effect on serum levels of ASAT and ALAT were found.

A fourth study, Riserius, Bergland & Vessby (2001) (Attached as Exhibit G) of CLA supplementation for 4 weeks in 25 obese men with metabolic syndrome was conducted and reflects the same pattern as the studies discussed above. The CLA capsules were well-tolerated in all patients in this randomised, controlled trial, with no adverse events clinically detected or reported.

ii. Long term study:

The treatment period for the abovementioned studies, however, does not exceed 3 months duration. To overcome this another Norwegian study (CLA006) was started in March 2001. The study included180 moderately overweight subjects enrolled at two Norwegian centers in order to assess the efficacy and safety of CLA when given for 12 months, either in the form of triglycerides or free fatty acids, and compared to a third group given placebo (olive oil).

The safety results up to now, (cut-off point: May 21' 2002) where 98 patients have completed the trial, 70 subjects with approx 10.5 months in the trial and 22 drop-outs at different time points, are based on roughly 165 patient years' exposure to the investigational products; 110 to CLA and 55 to placebo. Of 22 patients withdrawn 6 have been lost to follow-up, 4 have left the trial due to musculo-skeletal adverse events, while 4 patients have suspended trial supplement due to abdominal discomfort (2), diarrhoea (1) and nausea (1), all judged "probable" as per relationship to the regimen(s)rested. Of 232 single events, 33 have been regarded as supplement related (Probable : 9 events (3.9%) and Possible: 24 events (10.3%)). The supplement-related AEs most likely to occur originate from the gastrointestinal system. Its hardly surprising that ingestion of 4.5 g oil daily (3.4 g CLA + other oil constituents) given in six rather bulky capsules might precipitate symptoms of indigestion in a few subjects.

However, the severity of symptoms has been mainly mild and transient by nature. The events grouped as "metabolic/nutritional" show no sign of causality by CLA or placebo. The occurrence of disorders of the endocrine system in females is confined to four registrations of elevated TSH and four cases of "hypothyroidism". Of the cases, seven are labelled "Possible" and have been subject to laboratory re-testing. In three cases the condition was resolved after one month, in 3 cases the condition persists at end of last visit so far, and for one case no outcome is given. Even though the incidence of mild hyothyroidism appears to be higher in this study than in a corresponding cohort of subjects matched for age, the subjects have not been withdrawn, but have chosen to continue until the end of the trial.

No efforts to ascertain causality by the challenge have been tried. One case of osteoporosis has been diagnosed during the trial, however the investigator is inclined not to see any connection between the event and the trial preparation(s).

The four serious adverse events (SAEs) observed during the trial so far are not related to the use of trial supplement(s) Three cases are due to injury or elective surgery and one case because of pregnancy (withdrawn from trial).

Though care should be shown when drawing conclusions from material collected for the cause of a cut-off-date instead of waiting for the frozen data at trial end, the incidence of adverse events in this trial, grouped by origin and organ affinity, does not seem to deviate far from the pattern observed in a matched group of non-treated subjects.

C. Conclusion Concerning Saftey Of CLA:

Hitherto the most comprehensive safety profile of CLA in humans is based on results from a number of short-term clinical trials. The results from the CLA006 study which is meant to fill the gap of long-term safety, will soon be properly analyzed and reported. However, the trial as such, has not brought out side effects of an unexpected and serious nature that could indicate a harmful or detrimental effect of the regimens used.

IV. NATURAL ASA's Technical Representative Contact Information:

Hogne Vik
Natural ASA
Kjorbokollen 30
N-1337 Sandvika
Norway
hogne@natural.no
Phone: + 47 97 53 53 26
Fax: + 47 67 81 72 01

Please do not hesitate to contact the above identified representative of Natural ASA or me directly if FDA has any questions or requires additional information regarding this NDI notification.

Very truly yours,

Jason S. Crush
Legal representative

and

Hogne Vik
Natural ASA Regulatory Officer

JSC/rs
Enclosures
2162