DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: OCT 17 2000

From: (Acting) Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification for New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient:	Troxerutin Complex
Firm:	Nutratech, Inc.
Date Received by FDA:	August 7, 2000
90-Day Date:	November 5, 2000

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on pubic display in docket number 95S-0316 after November 5, 2000.

Felicia B. Satchell

Felicia B. Satchell

95S-0316

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC

OCT 17 2000

Carl Germano, RD, CNS, LDN
Senior VP Product Development and Research
Nutratech, Incorporated
208 Passaic Avenue
Fairfield, New Jersey 07004

Dear Mr. Germano:

This is to inform you that the notification, dated July 25, 2000, you submitted pursuant to section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act was received and filed by the Food and Drug Administration (FDA) on August 7, 2000. Your notification concerns a combination of substances called "troxerutin complex" that you assert is a new dietary ingredient.

Your notification will be kept confidential for 90 days following the date of its receipt. After November 4, 2000, the notification will be placed on public display at FDA's Dockets Management Branch in docket number 95S-0316. However, any information that is trade secret or otherwise confidential commercial information in the notification will not be disclosed to the public.

Please contact us at (202) 205-4168, if you have any questions concerning this matter.

Sincerely,

Felicia B. Satchell

Felicia B. Satchell
(Acting) Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Nutratech

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July 25, 2000

Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, SW
Washington, DC 20204

Re: Troxerutin Complex

Dear Sir or Madam:

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, this submission responds to your letter of June 9, 2000. That letter responded to Nutratech's March 27, 2000 submission regarding TROXERUTIN. In this connection, Nutratech, Inc. proposes to market a dietary ingredient, Nutratech's TROXERUTIN COMPLEX, an oxerutin formulation of mono-, di-, tri-, and tetra-hydroxyethyl-3,4,5,7 rutosides of which troxerutin is the major component. TROXERUTIN COMPLEX is intended for use in dietary supplements at a level not to exceed 500 mg per day with meals and for no longer than 1 month. Enclosed are an original and 2 copies of this submission.

This submission provides additional safety data to that previously submitted. It provides a recommended daily dose limit and length of use limit that will be set forth on the TROXERUTIN COMPLEX raw material label and product specification. It states that troxerutin is not intended for chronic consumption in a dietary supplement. The safety of both troxerutin and oxerutin are also described, and the following comments from FDA's June 9, 2000 letter are addressed specifically:

- In response to the FDA comment that

  > *Only 4 studies specifically examined troxerutin and are relevant to establishing whether a dietary supplement containing troxerutin would reasonably be expected to be safe,*

  13 troxerutin and 19 oxerutin studies are included that substantiate that Nutratech's TROXERUTIN COMPLEX is reasonably expected to be safe under the conditions of use set forth above.[1]

- In response to the FDA comment that

  > *The studies that examined troxerutin in conjunction with other substances are not relevant to establishing whether a dietary supplement containing troxerutin would reasonably be expected to be safe, because they examined the use of troxerutin in conjunction with other substances,*

[1] To the best of Nutratech's knowledge, all studies bearing on the safety of troxerutin complex reasonably available to Nutratech have been provided in this submission and in Nutratech's prior submission.

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Nutratech does not rely on data generated regarding other substances, e.g. . . . coumarin, to show that troxerutin is safe; rather, these studies were included to demonstrate that the studies submitted do not raise any question about the safety of troxerutin.

- In response to the FDA comment that

> *...studies (cited) are not relevant to establishing whether a dietary supplement containing troxerutin would reasonably be expected to be safe, because they describe the results of studies of substances that are related to troxerutin but which have different pharmacologic actions,*

Nutratech's submission elaborates on the pharmacology and chemical structure of troxerutin and oxerutin. The relationship of oxerutin to troxerutin is explained—specifically, the fact that Nutratech's TROXERUTIN COMPLEX is a standardized mixture of hydroxyethyl derivatives of rutin, O-beta-hydroxyethyl-rutosides, known as oxerutin, of which the tri-7,3',4'-hydroxyethylrutosides (troxerutin, CAS 7085-55-4) is quantitatively the major component. This mixture is comparable to the products studied in clinical trials and presented in this submission.

- In response to the FDA comment that

> *...studies (cited) are not relevant to establishing whether a dietary supplement containing troxerutin would reasonably be expected to be safe because studies (are not) designed to provide data that are relevant to assess the safety of the chronic consumption of troxerutin in dietary supplement,*

It is explained that Nutratech's TROXERUTIN COMPLEX is intended for use for no more than 1 month.

- In response to the FDA comment that

> *...studies (cited) are not relevant to establishing whether a dietary supplement containing troxerutin would reasonably be expected to be safe because they are short duration studies,*

Various studies are provided that far exceed the 1-month length of time recommended by Nutratech for use of Nutratech's TROXERUTIN COMPLEX.

- In response to the FDA comment that

> *...studies (cited) are not relevant to establishing whether a dietary supplement containing troxerutin would reasonably be expected to be safe because (they) describe the effects of its non-oral use...(ie, IM and IV),*

We explain that these studies were included to provide pharmacokinetic data, not to substantiate the safety of the oral route.

- In response to the FDA comment that

> *...studies (cited) are not relevant to establishing whether a dietary supplement containing troxerutin would reasonably be expected to be safe because (they) do not include clinical measurement that allow its effects to be evaluated,*

These studies were included to demonstrate that no adverse effects were noted during this study.

- In response to the FDA comment that

> *...studies (cited) are not relevant to establishing whether a dietary supplement containing troxerutin would reasonably be expected to be safe because (they) use patients with underlying diseases which raise questions about their relevance to examining the effects of the substance in healthy humans,*

Studies in healthy humans, including 2 studies in pregnant women, are provided.

As a dietary supplement, Nutratech's TROXERUTIN COMPLEX will be marketed as a powder and labeled with a recommended dose of 500 mg per day orally (1/2 the dose typically used in studies) for no longer than 1 month (less than the typical amount of time reported in studies).

In addition, TROXERUTIN COMPLEX is not intended for use by pregnant or lactating women and will be so labeled.

If you have any questions, please contact us or Nutratech's counsel, Anthony L. Young, Piper Marbury Rudnick & Wolfe LLP, 1200 19th Street, NW, Washington, DC 20036, (202) 861-3882; fax (202) 223-2085; email: anthong.young@piperrudnick.com. We would appreciate the opportunity to discuss this submission and the conditions of use recommended for TROXERUTIN COMPLEX.[2]

Yours truly,

Carl Germano, RD, CNS, LDN
Senior VP Product Development & Research
Nutratech, Inc

Janice Roma Kane, DO
Product Development & Research
Nutratech, Inc

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[2] In its initial submission, Nutratech noted that troxerutin is presently on the market in the United States as a dietary supplement. Nutratech is investigating whether troxerutin was marketed in the United States prior to October 15, 1994.

TROXERUTIN COMPLEX—Oxerutin Containing 50% Troxerutin

This submission is in response to FDA's letter of June 9, 2000 regarding Nutratech, Inc's plans to market the dietary ingredient TROXERUTIN COMPLEX. This document provides additional safety data. It addresses the recommended dose and duration of use for troxerutin and the fact that troxerutin is not intended for chronic consumption in a dietary supplement. The safety of both troxerutin and oxerutin are also described, and FDA comments are addressed specifically.

Background: Bioflavonoids & Rutin

Bioflavonoids, also known as flavonoids, are a class of water-soluble plant pigments. They are one of the most numerous and widespread groups of natural compounds and are found in foods, such as citrus fruits, onions, and soybeans. They are ubiquitous in all major groups of green plants.[1] Some of the most well known bioflavonoids are isoflavones, genistein, quercetin, hesperidin, and rutin. Rutin is a crystalline glucoside of quercetin, closely related to hesperidin. This phenolic compound is found in many plants, including buckwheat, eucalyptus leaf, rosehips, blue violet leaf, forsythia, hydrangea, and pansies.[2] Like other bioflavonoids, rutin has a very low toxicity. Rutin is on the National Nutritional Foods Association list of dietary supplement ingredients in use before October 15, 1994.

Troxerutin & Oxerutin

Troxerutin is a rutin (rutoside) that has been used therapeutically worldwide for more than 30 years to address chronic venous insufficiency (CVI), varicosity, and capillary fragility. Oxerutin (O-beta-hydroxyethyl-rutosides) is a standardized mixture of hydroxyethyl derivatives of rutin, of which the tri-7,3',4'-hydroxyethylrutosides (troxerutin, CAS 7085-55-4) is the quantitatively major component.[3] This hydroxyethyrutoside preparation contains mono-, di-, tri-, and tetrahydroxethyl of rutin, specifically 3',4',7'-tri-O-(beta-hydroxyethyl)-rutoside (troxerutin); 3',4',5-tri-O-(beta-hydroxyethyl)-rutoside; 3',4',5',7'-tetra-O-(beta-hydroxyethyl)-rutoside; 4', 7'-di-O-(beta-hydroxyethyl)-rutoside; and 4'-mono-O-(beta-hydroxyethyl)-rutoside.[4] **Said simply, TROXERUTIN COMPLEX *is* oxerutin, which is a mixture of derivatives of rutin of which troxerutin is the major component.**

The troxerutin formulation submitted by Nutratech, Inc to the FDA in its dietary ingredient notification is produced by hydroxethylation of rutin. In addition to trihydroxethyl of rutin (troxerutin) it also contains mono-, di-, tetrahydroxethyl of rutin.

Because troxerutin is the predominant component in the oxerutin formulation (ie TROXERUTIN COMPLEX), the chemical and commercial names for troxerutin and oxerutin are frequently used interchangeably. This practice can be a cause for confusion and has even been adopted by the National Library of Medicine[5] and France's *Banque De Donnees Sur Les Medicaments* (BIAM)[6]. An additional source of confusion is the fact that the percentage of troxerutin found in oxerutin varies slightly with each manufacturer. When Rehn and colleagues conducted a study comparing equivalent doses of oxerutin and troxerutin, troxerutin was 40% of the oxerutin preparation.[3] In related studies, Nocker used an oxerutin preparation containing 94% troxerutin.[3] **BIAM* cites 50% to 58% as a standard for the percent of troxerutin contained in oxerutin. The Nutratech formulation contains 50% to 60% troxerutin plus a combination of**

mono-, di-, and tetra-hydroxyethyl-3,4,5,7 rutosides in proportions comparable to the other formulations on the market. Accordingly, Nutratech's TROXERUTIN COMPLEX is comparable to products studied in clinical trials[6] and presented in this document.

TROXERUTIN (TRI-HYDROXYETHYL-3',4',7 RUTOSIDE)

- ***Troxerutin was not mutagenic in* in vitro *testing, even in high doses.***
- ***Troxerutin had an excellent safety and tolerability profile in numerous clinical trials, even with high doses.***
- ***Troxerutin has been the subject of numerous clinical trials, animal studies, and* in vitro *studies.***

In a study conducted by Marzin and colleagues, troxerutin clearly showed an absence of any mutagenic activity. When used with the *Salmonella typhimurium* tester strains TA1535, TA1537, TA 1538, and TA100, troxerutin did not cause a significant increase in any revertants at any doses tested. Although troxerutin was a very weak cytotoxic agent, it was more than 500 times less cytotoxic when compared with quercetin. In the test of point mutation using V79 cells, troxerutin was not mutagenic, although high doses were used. In the *in vitro* human lymphocyte test, troxerutin had no clastogenic activity, although studied at 10 mg/ml with and without metabolic activation. There was a small increase in the number of cells with aberrations excluding gaps, but it was not statistically significant.[7]

Troxerutin has been the subject of numerous clinical trials, animal studies, *and in vitro* studies. In all these clinical trials, troxerutin has had an excellent safety and tolerability profile, even when taken in high doses. In a French study of 26 pregnant women with clinical symptoms of CVI of the lower limbs, 12 women received troxerutin

4 grams per day and 14 received placebo for 30 days. One woman had transitory diarrhea and 1 woman had a moderate case of gastritis that resolved without treatment during the study.[8] In another study, the effect of troxerutin on fibrinolysis and hemorheology was investigated in 85 patients with CVI. Although there were 5 withdrawals from the troxerutin group and 5 from the placebo group during the 5-day trial, all were for reasons unrelated to treatment.[9]

In a double-bind trial of the efficacy of troxerutin in CVI conducted by Vin and colleagues, 34 patients with truncal varicose veins received troxerutin **3500 mg daily** for 2 months and 35 received placebo. The criteria of inclusion were primary truncal varicose veins or post-thrombotic, single or bilateral, with ostial reflux on Doppler exam and subjective symptoms of venous origin.[10] All participants were non-smokers.[10] Exclusion criteria were arteriopathy, osteo-articular disease, diabetes, acute or chronic inflammatory syndrome, hemopathy, and treatment with an anticoagulant or platelet antiaggregants, diuretics, NSAIDS, veinotonics or any drug that can interfere with hemo-rheologic parameters or venous tonus.[10] A history of superficial or deep venous thrombosis, within 2 to 18 months, respectively, as well as sclerotherapy or recent stripping, excluded a candidate. Five patients dropped out during the run in period, and 4 withdrew during the first 60 days.[11] One individual in each group withdrew because of nausea, 1 in the placebo group dropped out because of ineffective treatment, and 1 in the troxerutin group for reasons unconnected to the trial. Overall, tolerance to the treatment was good. There were 5 cases of minor digestive disturbances, but these complaints did not warrant modification in dosing or discontinuation of therapy. Troxerutin had a good safety profile. There were 5 cases (3 troxerutin and 2 placebo) of minor gastrointestinal side effects that did not require modification of treatment.[11] Vin had also conducted a similar double blind, placebo-controlled troxerutin efficacy study 2 years previous.[10]

Incandela and colleagues conducted a double-blind, placebo-controlled, 8-week study to investigate the effects of troxerutin on CVI. Thirty patients from 30 to 80 years old received placebo or troxerutin 300 mg/day for 8 weeks. No side effects occurred during the study or within 6 weeks after the study ended.[12] A prospective, randomized, double-blind study designed by Glacet-Bernard to evaluate the effect of troxerutin on retinal vein occlusion enrolled 27 patients with central retinal vein occlusion and 26 with branch retinal vein occlusion. Participants were randomly assigned for treatment with either troxerutin **7 grams per day** or a placebo for 4 months. Of the 62 patients enrolled, 9 were excluded. The medication was discontinued in 2 patients in the troxerutin group and 1 in the placebo group because of digestive disturbances. Three patients in the placebo group experienced a severe intercurrent disease that required their exclusion, and 3 other patients (1 in the troxerutin and 2 in placebo) chose to discontinue the medication. The mean long-term follow up for patients in the troxerutin group was 23 months.[13]

A placebo-controlled, multicenter, parallel-group study conducted by Steru and Steru evaluated troxerutin in regard to efficacy and tolerance in the treatment of CVI, heavy legs, and idiopathic lower limb edema.[14] The study population included 186 participants, predominately women, with an average age of 44 years. All patients complained of heaviness of 1 or 2 legs, with a median intensity of 63 on a scale of 100. Eighty percent had leg pain with an average intensity score of 50, and close to

80% had edema. The women took troxerutin **2000 mg per day** or placebo for 2 months. Tolerance to troxerutin was excellent and the only secondary effects were some benign cases of digestive intolerance.[14]

Gueguen-Duchesne and colleagues enrolled 20 patients with moderate hypertension between 42 and 62 years old in a hemorheological study of the effects of troxerutin. Individuals with diabetes, coronary heart disease, renal insufficiency, severe hypertension, or dyslipidmia were excluded, as were those using vasoactive drugs, platelet antiaggregants, anticoagulants, rheological drugs, or hypertensives. There was no difference in whole blood and erythrocyte filtration and ATP values between the study group and controls on day 1, but blood and plasma viscosities were significantly higher in the study group. Participants took troxerutin **3000 mg per day** in 3 doses for 4 weeks.[15] Biochemical monitoring was focused on possible risk factors, and results showed that sodium, potassium, glycemia, creatinine, uric acid, cholesterol, triglycerides, immunoglobulins, were unchanged compared with controls. There was no significant variation in fibrin in individuals with normal values on day-0, however there was a 40% decrease in fibrin in those with values that were initially higher than average. In the troxerutin group, mean blood pressure decreased from 122+12 on day 0 to 110+15 on day 45 ($p<0.001$); and blood and plasma viscosities, and blood aggregates decreased.[15]

In a study to learn the effects of high-dose troxerutin, Boisseau and colleagues recruited 7 women with uncomplicated CVI. Two women were under 40 years old and 5 were over 50. Five had varicose veins with no ulceration, and none had deep vein thrombosis. All had pain and heaviness in the legs, and 2 had edema. Participants received troxerutin **3 grams per day** orally for 3 weeks. Results showed no notable anomalies in hemorheologic parameters, and hematocrit and the fibrinogen were normal. There was a slight increase of the middle rate of the leukocytes, more accentuated in certain patients, but investigators speculated that this action of leukocyte demargination was secondary to flavones. The clinical tolerance of the product was excellent for all women except one who experienced some poorly defined digestive complaints.[16]

Marhic conducted a double-blind, placebo-controlled trial of troxerutin designed to treat 60 women with vulval varicosity and venous insufficiency of the lower limbs, half in the context of premenstrual syndrome and half in pregnant women from the 4th month on. Patients were treated with troxerutin **4 grams** or placebo administered twice per day from the 6th to the 25th day of their cycle. During this 4-month trial, tolerance to troxerutin was excellent.[17]

OXERUTIN (TROXERUTIN COMPLEX)

- ***Oxerutin is a standardized mixture of hydroxyethyl derivatives of rutin of which troxerutin is the major component.***
- ***Oxerutin has been well tolerated in numerous clinical trials.***
- ***Adverse events with oxerutin are mild, transient, and rare.***

Oxerutin has been well tolerated by patients participating in numerous clinical trials. Most adverse events have been mild and transitory.[18] Patients with CVI most frequently reported GI disorders, headache, dizziness, and pruritus, and patients with hemorrhoids

reported GI disturbances most often.[18] However, the incidence of adverse events was similar in the oxerutin and placebo groups.[18] In a study conducted by Bergquist and colleagues in 1981 of 149 patients with CVI, the incidence of individual adverse events in oxerutin treated patients was 4% to 24%, and in placebo recipients it was 3% to 20%. Fewer than 5% of oxerutin recipients reported vomiting (1.3% vs 0 placebo), diarrhea (4% vs 12% placebo), or sleep disorders (0 vs 4% placebo), and the only adverse event-related withdrawals (n = 2) were from the placebo-treated group. A review article by Wadworth and Faulds cites several studies. In one study conducted by Quigley and Faris in 1991, 2 patients with severe CVI withdrew due to pruritic rash and 1 due to diarrhea. Two patients participating in studies conducted by de Jongste reported hair loss. In 1972, Pterovsky reported skin eruptions, diuresis, increased appetite, late menstruation, 'heavy head', and abnormal laboratory values in 2% of patients treated with either oxerutin or placebo that were not attributed to treatment.[18]

In a double-blind study to compare the efficacy and tolerability of oxerutins with troxerutin, 12 post-menopausal women with grade II CVI were enrolled by Rehn.[3] They received **900 mg per day** oxerutins or troxerutin for 12 weeks.[3] Both compounds were well tolerated and there were no adverse events reported with either treatment.[3] Similar results were reported in Nocker's larger dose-finding studies with oxerutins in similar patients using the same technique with treatment of 3 weeks[3,20] and 12 weeks.[20] In a study conducted by Rehn and colleagues, 16 healthy volunteers took either oxerutin **1000 mg per day** for 3 weeks or placebo. Results showed no abnormal laboratory values for participants. Gamma-GT, GOT, GPT, creatinine, blood glucose, hemoglobin, erythrocytes, and leukocytes were within normal limits with respect to pretreatment values after placebo and oxerutin treatment. There were no adverse drug effects.[21] Rehn also conducted an oxerutin dose-finding study. He and his colleagues enrolled 100 women with CVI grade II in a randomized, placebo-controlled, parallel group trial. Following a 2-week run-in phase, patients were treated for 12 weeks with oxerutin **900 mg to 1000 mg per day**.[22]

Nocker and Diebschlag conducted a preliminary 3-week double-blind versus placebo study to evaluate dose-response effect and efficacy of oxerutin oral solution. The women with CVI grade II who were enrolled in the study were tested with oxerutin quantified in various dosages. In a second, larger 3-month study, Nocker and Diebschlag compared **600 mg-, 900 mg-, 1200 mg- and 1500 mg-** doses of oxerutin.[20] Thirty menopausal women ≤60 years of age, diagnosed with CVI grade II were enrolled in a 12-week study.[20] Individuals treated within 8 days of the study with venous pharmaceuticals, anti-inflammatories, corticosteroids, or diuretics, or who had edema unrelated to venous edema, were not accepted into the study. Participants received either oxerutin 600 mg-, 900 mg-, 1200 mg-, or 1500 mg- or placebo. After the 16th week a follow-up examination was carried out in order to find out about possible continued effects of oxerutin past the treatment duration. Six menopausal women were each treated with 600 mg-, 900 mg-, 1200 mg-, and 1500 mg- or placebo-oral solution.[20] There were no differences from group to group regarding patient structure, disease and diagnosis. The simultaneous comparison of all dosages at the end of the 3-month treatment showed no significant differences regarding its effectiveness between the oxerutin groups. The digestibility was judged as "very good" to " good" in the placebo-group and in the groups with active ingredient mostly as "good". No side effects were reported.[20] In 1994, Diebschlag and colleagues compared 2 doses of oxerutins to placebo in a 16-week study. The purpose of the study was to compare the efficacy of oral doses of 500 and 1000 mg per day. Sixty postmenopausal women with primary varicosity or post thrombotic syndrome

participated in a double-blind, placebo-controlled study. Those with edema of non-venous origin or peripheral arterial disease of heart, hepatic, or renal failure were excluded. All 60 women completed the study. There was a 100% mean compliance with no significant differences between the treatment groups. Results showed that all treatments were well tolerated. One patient in the 1000-mg group had transient GI discomfort of unclear causaltity.[23]

In Indonesia, 97 women with first-, second-, or third-degree hemorrhoids of pregnancy were given either oxerutin **1000 mg per day** or placebo. Side effects were mild and transient, and there were no oxerutin-related problems in the pregnancy or delivery. The tolerability was excellent with only 3 patients exhibiting minor and transient side effects: one woman experienced abdominal discomfort and palpitations and 2 reported dizziness. These side effects were all reported after 2 weeks of treatment and diminished spontaneously after 4 weeks without specific treatment. Of the 97 patients, 92 had a normal pregnancy, delivery, and baby. The placebo group had 1 intrauterine fetal death, 1 premature delivery, and 1 baby small for gestation age. The oxerutin group had 1 premature delivery and 1 polydactyly, a congenital anomaly. Because the mother of the child with the congenital anomaly was 32 years of age and began treatment with troxerutin in the 34th week of pregnancy (at a time when organogenesis would have been completed), the abnormality was considered not related to oxerutin treatment.[19]

A 4-week study designed by Renton and colleagues to measure the effects of oxerutin **2 grams daily** on edema and paresthesia of the ankle and foot, reported no side effects in the 40 patients who participated. Although 25% of the patients dropped out of the trial, the causes were unrelated to treatment.[24]

Oxerutin **900 mg per day** was very well tolerated in a 6-month study of 102 patients over 65 years old with CVI, conducted by MacLennan and colleagues. Both adverse events and laboratory measurements were comparable in the oxerutin group and placebo group. Forty-two patients reported 51 adverse events—26 in the oxerutin group and 25 in the placebo group. Adverse events resulted in withdrawal from the trial in 11 cases—3 in the oxerutin group and 8 in the placebo group. The other cases were evenly distributed between the 2 groups. Thirty-one laboratory measurements were made 3 times to evaluate tolerability. Of this total, a transition of a value from within to without the normal range was seen in 144 tests related to 59 patients—65 abnormal transitions in 28 patients in the oxerutin group and 79 abnormal transitions in 31 patients in the placebo group. Statistically significant variations in the oxerutin group were decreases in hematocrit, red cell count, and beta-globulin, and an increase in prothrombin. In the placebo group there was an increase in urea levels. The investigators judged none of these changes as severe or related to the trial medication.[25]

A randomized, double-blind, cross-over trial was performed on 26 patients with postmastectomy lymphedema of the arm, and 14 with lymphedema of the leg.[26] In a 6-month study conducted by Piller and colleagues, patients took oxerutin **3 grams per day**, and 70% of participants preferred the effects of the active drug.[26]

In a multi-center clinical trial designed to assess the efficacy and safety of oxerutin, 101 patients with post-thrombotic syndrome took oxerutin **1200 mg daily** or placebo for 8 weeks. Oxerutin was well tolerated in most patients. In the oxerutin group, 7 patients experienced either headache, hair-loss, swollen legs, swollen fingers, muscle stiffness, skin rash, or dizziness. In the placebo group, 5 patients experienced either neck pain,

urinary frequency, skin rash, or headache. The only dropout was a patient in the placebo group who stopped after the 4th week.[27]

TROXERUTIN-COUMARIN COMBINATION PRODUCTS

- ***Coumarin in Food or Cosmetics Poses No Health Risk To Humans***

A combination of 6 parts troxerutin plus 1 part coumarin (2, H-1-benzopyran-2-one) is marketed in Europe. Coumarin (CAS 91-64-5) has been used as a fixative and flavoring agent in foods and as a pharmaceutical excipient. Because it produced liver toxicity in animals, it was re-categorized by the United States Food and Drug Administration (FDA) as a food adulterant in 1954. There are little toxicity data on long-term treatment with coumarin. The common adverse effects associated with coumarin are mild nausea and diarrhea, and there are rare idiosyncratic liver toxicity reported. Coumarin-induced hepatotoxicity is highly variable between species.[28] The maximum daily human exposure to coumarin from dietary sources and fragrance in cosmetic products is 0.06 mg/kg per day. No adverse effects of coumarin have been reported in susceptible species in response to doses that are more than 100 times the maximum human daily intake.

More that 40 studies have investigated troxerutin in combination with coumarin, providing a large body of data demonstrating the safety of troxerutin plus coumarin. **However, our data do not rely on these studies with coumarin, to show that troxerutin is safe. Rather, they were included to show that these studies do not raise any question about the safety of troxerutin.** There were no side effects experienced by 16 chronic schizophrenics who were treated for 3 months with troxerutin plus coumarin or a placebo in a randomized, double-blind, crossover trial conducted by Casley-Smith and colleagues.[29] When Krajnovic examined the hematological parameters of erythrocytes, hemoglobin, thrombocytes, thrombelastogram, prothrombin time, blood-clotting, and bleeding time in 20 mothers and their infants, after administration of troxerutin plus coumarin, a combination of coumarin and troxerutin, all values tested were within normal ranges before and after treatment.[30]

In a teratogenic and embryotoxic side-effects study conducted by Grote and colleagues, pregnant Göttingen miniature pigs were given a combination of troxerutin and coumarin, orally at 100-fold the therapeutic dose (troxerutin 150 mg/kg per day plus coumarin 25 mg/kg per day) from day 6 to day 30 of gestation. There was no embryotoxic or teratogenic damage caused by the tested combinations. Morphological and chemical tests showed no findings definitely attributable to the compound.[31]

Preuss-Ueberschar and colleagues found no reproduction toxicological risk with a troxerutin plus coumarin in a combined study of 3 generations of SPF Wistar rats evaluated on the fertility and teratogenicity, as well as peri- and post- natal development. One-, 8-, 64-, and 128-fold of the human daily therapeutic dose was suspended in tap water and administered orally by gavage to 95 male and 190 female rats in 4 test groups. Twenty-three male and 46 female rats were given tap water alone. The male animals were subjected to a pretreatment of 10 weeks, the female animals to a pretreatment of 3 weeks. The treatment was continued during mating. The animals scheduled for cesarean section received the test substance until the day of the laparatomy (gestation day 20), those selected for littering throughout lactation (day 24 postpartum). In 1 test group, there was a decrease in food consumption and a reduction

in weight gain, as well as dose-related hepatic lesions. The test substance had no effect on either the treated P generation or the untreated F1 generation.[32]

In a study conducted by Pulsford and colleagues, a 6:1 mixture of troxerutin plus coumarin, was given orally to baboons in doses of 100, 300 and 1000 mg/kg per day for 26 weeks. Vomiting of central origin, usually within 3 hours of administration and vomiting immediately after dosing, was seen in animals receiving 1000 mg/kg per day. At this level, 2 animals collapsed on several occasions, 1 of whom died. Another animal receiving 1000 mg/kg per day was killed following a period of weight loss, reduced appetite, and deterioration in body condition. There were no adverse effects on weight gain, food or water consumption, or ophthalmoscopic or electrocardiographic examinations in any other animals during the study. Serum leucine aminopeptidase, and serum ornithine carbamyl transferase levels were increased during the dosing period, together with slightly increased liver weights at autopsy for animals receiving 1000 mg/kg per day. Because there were no morphological or ultrastructural changes, investigators attributed the changes in the liver to hypertrophy.[33]

DOSE CONSIDERATIONS

- ***Troxerutin and oxerutin have been the subject of numerous clinical trials, animal studies, and* in vitro *studies.***
- ***In clinical trials, troxerutin has been given in doses up to 7 grams per day orally for up to 4 months.***
- ***In clinical trials, oxerutin has been given in doses up to 3 grams per day orally for up to 6 months.***
- ***The recommended daily dose of TROXERUTIN COMPLEX is approximately 1/3 of the recommended therapeutic dose for oxerutin and approximately 1/10 of the recommended therapeutic dose for troxerutin.***

Troxerutin Dosing in a Therapeutic Setting

The recommended therapeutic dose for troxerutin is 2000 to 3500 mg per day.[34] Troxerutin has been given in clinical trials for up to 6 months in doses up to 7 grams per day. Marhic and colleagues, gave a dose of 4 grams daily without clinical consequence to women at least 4 months pregnant.[17]

Oxerutin Dosing in a Therapeutic Setting

For patients with CVI or hemorrhoids, the recommended oxerutin oral dosage is 0.9 to 1.2 grams per day.[18] The recommended daily dosage is 3 grams for patients with lymphedema, and 1.2 to 2.4 grams for patients with diabetic retinopathy.[18]
Oxerutin has been given in clinical trials for up to 6 months in doses up to 3 grams per day (Table 1). The typical therapeutic dosing schedule for oxerutin is 250 mg 3 to 4 times per day, initially for 3 weeks, followed by a maintenance dose of 250 mg 1 to 2 times per day (Table 2A).

Troxerutin & Oxerutin Dosing as a Dietary Supplement,

Doses for troxerutin, used as a dietary supplement, were calculated after an assessment of animal and human clinical trial data. **As a dietary supplement, TROXERUTIN**

COMPLEX will be marketed as a powder with a recommended dose of 500 mg per day orally for no longer than 1 month. Troxerutin is not intended for use by pregnant or nursing women and will be so labeled.

- **The recommended daily dose for TROXERUTIN COMPLEX as a dietary supplement is 500 mg per day.**
- **A 500-mg dose of TROXERUTIN COMPLEX is 17% to 50% of the recommended therapeutic dose for oxerutin and 10% to 12% of the recommended therapeutic dose for troxerutin.**
- **A 500-mg dose of TROXERUTIN COMPLEX is 15% of the maximum dose given in a clinical trial for oxerutin and 4% of the maximum dose given in a clinical trial dose for troxerutin.**
- **The recommended daily dose of TROXERUTIN COMPLEX as a supplement is approximately 1/3 the recommended therapeutic dose for oxerutin and approximately 1/10 of the recommended therapeutic dose for troxerutin.**

SUMMARY

Oxerutin and it major component, troxerutin, have been used safely worldwide for more than 30 years to treat CVI, capillary fragility, and varicosity. To date, troxerutin and oxerutin have been the subjects of numerous clinical trials (including a study with pregnant women), animal studies, and in *in vitro* studies. Clinical trials have used doses of 100 mg to 7000 mg per day orally for up to 6 months. Throughout these trials, troxerutin and oxerutin had an excellent safety profile and were well tolerated, even in high doses. *In vitro,* troxerutin clearly showed an absence of any mutagenic activity. Adverse events with troxerutin and oxerutin are rare; and when they occur, they have always been mild, and transient. The side effects usually seen are benign cases of digestive intolerance that do not require any changes in treatment.

Today, oxerutin and troxerutin are on the market in Europe, Africa, South America, Australia, and New Zealand. Troxerutin is on the market in the United States. Although troxerutin, the major rutin in TROXERUTIN COMPLEX, is sold in the United States, Nutratech has decided to do an FDA submission. Based on the foregoing information, Nutratech firmly believes that TROXERUTIN COMPLEX is reasonably expected to be safe under the condition of use recommended in the labeling that Nutratech will use for this dietary ingredient.

APPENDIX

Pharmacological profile

*Oxerutin acts mainly on the microvascular endothelium where it reduces hyper permeability and edema. In healthy volunteers, and patients with CVI, lower limb edema, idiopathic edema or diabetic microangiopathy, single doses of oxerutin 0.3 to 1 gram orally or intravenously (IV) reduce capillary filtration rate. In addition, oral dosages of 1 to 3 grams daily have improved parameters of microvascular perfusion, including transcutaneous p02, and have reduced edema formation in patients with CVI. Oral and IV administration of 3 grams per day decreases microvascular permeability in patients with severe venous hypertension and patients with diabetic microangiopathy. Oxerutin inhibits erythrocyte aggregation in healthy volunteers and preserves erythrocyte deformability in patients undergoing cardiac valve replacement. Oxerutin attenuates nicotine-induced endothelial cell damage in healthy volunteers, and in animals, it has inhibited free radical scavenging. The preparation also appears to have an affinity for vein walls with a possible protective effect against endothelial cell damage and hydroxyl radical formation...Data from studies in healthy volunteers show that the proportion of a dose of oxerutin reaching the systemic circulation is low; about l0% of an orally administered dose is absorbed. In healthy volunteers peak plasma oxerutin concentrations are reached within 1 to 6 hours of oral administration. A maximum plasma concentration of 142 mg/l was reached following a single oral 900-mg dose. The plasma elimination half-life ranges from 10 to 25 hours after oral administration and is approximately 1 hour after intravenous administration. The components undergo degradation by intestinal flora to aglycones, although mono-, di- and tri-hydroxyethylrutosides may undergo hepatic metabolism and are eliminated primarily via the bile. Three percent to 6% of an orally administered dose is excreted in the urine.**

***Adapted from Hydroxyethylrutosides: *A Review of its Pharmacology, and therapeutic Efficacy in Venous Insufficiency and Related Disorders* by Alison N. Wadworth and Diana Faulds**

Mechanism of Action

The major route of oxerutin excretion in both animals and humans is via the biliary-enteric route.[4] Troxerutin shows an affinity for the medial and outer regions of the venous wall with the highest uptake in the outer wall. Troxerutin was significantly accumulated in both inner and outer parts of the venous wall, but inner wall troxerutin uptake resulted from direct diffusion through the lumen, the outer wall uptake was likely from the vasa vasorum circulation.[34]

Troxerutin exerts its effects in venous insufficiency via actions on vessel walls and plasma cells. This is particularly marked at high doses.[35] In clinical trials, troxerutin has exhibited a direct action on red cell aggregation, particularly marked at high doses. Troxerutin has both a direct rheological action and an effect on vessel wall. Troxerutin improves venous flow, lowers capillary resistance. It also ameliorates inflow to the microcirculation by reducing red cell hyperaggregation. Boisseau opined that it acts at the conjunctival level by enhancing both absorption of catabolites on proteglycans, and tone (higher ATP levels in smooth muscle cells).[35] It has been shown to affect

erythrocyte aggregation in vitro. In vivo, Dufaux has demonstrated that it improves microcirculatory flow in the rat treated with Dextran to induce hyperaggregabilty.[36] In man, troxerutin has been found to reduce post-operative erythrocyte sedimentation, and to improve blood filterability. Recently, blood viscosity and red cell aggregation have been studied after treatment with high doses (4grams per day) of troxerutin. A significant fall in viscosity at low shear rates was observed in the treated patients. This parameter has been shown to depend largely on red cell aggregation. By sampling varicose blood, Le Devehat has demonstrated that troxerutin has a local action. Taken together, these results are in favor of direct action of the drug on erythrocyte aggregation.[35]

Troxerutin has an influence on cellular interactions and has been shown to have an action on varicose ulceration, which is affected by microcirculatory impairment. It may act directly on aggregation, especially at high doses, via an effect on vascular permeability, which in turn reduces hemoconcentration and protein imbalance. In fact varicose hematocrit has been found to be reduced after treatment with troxerutin. It probably has a direct action on red cell physiology and/or action at the red cell membrane plasma interface. It is also thought to have action on red cell vessel wall interactions.[35]

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Table 1. **Troxerutin** 3',4',7-Tris(hydroxyethyl)rutin

Author	Title of study	Dose range	Duration	Patients	Safety Results
Boisseau[9]	Fibrinolysis and hemorheology in chronic venous insufficiency: a double blind study of troxerutin efficiency.	High-dose troxerutin	15 days	85	10 withdrawals: 5 from treatment, 5 from placebo. All for reasons unrelated to treatment.
Boisseau[16] Boisseau[35]	Erythrocyte aggregation and parameters hemorheologic at the insufficient venous influence of the troxerutin. Pharmacological aspects of erythrocyte aggregation, effect of high doses of troxerutin.	Troxerutin 3 grams/day	3 weeks	7 women	Clinical tolerance was excellent for all women except 1 who experienced some poorly defined digestive complaints.
Glacet-Bernard[13]	A randomized, double-masked study on the treatment of retinal vein occlusion with troxerutin.	Troxerutin 7 grams/day	4 months	62	9 withdrawals: 3 from treatment, 9 from placebo. Of the 9 withdrawals 2 experienced digestive disturbances and the remaining reasons were unrelated to treatment.
Gueguen-Duchesne[15]	Effects of Troxerutin on the hemorhhological parameters of patients with moderate arterial hypertension.	Troxerutin 3000 mg/day	4 weeks	20	Biochemistry measurements remained unchanged in time and as compared to the control group.
Incandela[12]	Efficacy of Troxerutin in patients with chronic venous insufficiency: a double-blind, placebo-controlled study.	Troxerutin 3500 mg	8 weeks	30	All patients completed the study. No side effects occurred during the study or within 6 months after the study ended.
Lefebvre[8]	Insuffisance veineuse de la femme enceinte: correction rheologique par la troxerutine.	Troxerutin 4 grams/day	30 days	26 pregnant women	Patients reported 1 case of transitory diarrhea, 1 case of gastric burning that regressed without treatment during the course of the trial.
Krajnovic[30]	The influence of the combination of coumarin and troxerutin on infantile blood parameter in lactation period.	Troxerutin 360 mg/day	3 weeks	20 mothers & infants	All values tested were within normal ranges before and after treatment.
Marhic[17]	Clinical and rheological efficacy of troxerutin in obstetric gynecology.	Troxerutin 4 grams/day	4 months	60	Excellent acceptability and tolerance.
Rehn[3]	Comparison between the efficacy and tolerability of oxerutins and troxerutin in the treatment of patients with chronic venous insufficiency.	Troxerutin 900 mg/day or Oxerutin 900 mg	12 weeks	12	Both compounds were well tolerated and there were no adverse events reported with either treatment.
Steru[14]	Clinical assessment of a phlebotrope: Veinamitol Study.	Troxerutin 1000 mg	2 months	186	Tolerance was excellent. The only secondary effects amounted to some benign cases of digestive intolerance.

Vin[10] Vin[11]	Action Of The Troxerutin on clinical parameters, plethysmographics and rheologics of venous insufficiency of the lower limbs: A placebo controlled trial. Double blind trial of the efficacy of troxerutin on chronic venous insufficiency.	Troxerutin 3500 mg	2 months	69	Treatment was well tolerated and had a good safety profile. Five cases of minor digestive disorders did not warrant modification in dosing or discontinuation of therapy. Withdrawals were due to 1 case of nausea or reasons unrelated to treatment.

Oxerutin O-(Beta-Hydroxyethyl)-Rutosides

Author	Title of study	Dose range	Duration	Patients	Safety Results
Belcaro[37]	Evaluation of capillary permeability and microcirculation in patients with chronic venous hypertension treated with Venoruton by the vacuum suction chamber (VSC) device and laser-Doppler flowmetry.	Oxerutin‡ 3000 mg/day divided into 3 doses	2 weeks	12	Safety results not reported.
Casley-Smith[29]	Benzo-pyrones in the treatment of chronic schizophrenic diseases.	Oxerutin**‡ 3 grams/day	3 months	16	No side effects with the active substance.
de Jongste[27]	A double blind three center clinical trial on the short-term efficacy of 0-(beta-hydroxyethyl)-rutosides in patients with post-thrombotic syndrome.	Oxerutin 1200 mg/day	8 weeks	84	Mild side effects.
Diebschlag[23]	A clinical comparison of two doses of o-(beta-hydroxyethyl)-rutosides (oxerutins) in patients with chronic venous insufficiency.	Oxerutin* 500-1000 mg/day	16 weeks	60	All completed the study. All treatment was well tolerated. One patient in the 1000-mg group had transient GI discomfort of unclear causality.
Hackett[4]	Metabolism of hydroxyethylrutosides [HR]: metabolism of [14C]-HR in man.	Oxerutin**‡ 900 mg/day divided into 3 doses	8 weeks	3	Safety results not reported.
Lukjan[38]	The effect of HR (O-Beta-Hydroxyethylo-Rutoside, Oxerutin*) on the deformability of erythrocytes in patients with arteriosclerosis obliterans of lower limbs.	Oxerutin* IV 1000 mg/day	3 weeks	44	Safety results not reported.
MacLennan[25]	Hydroxyethylrutosides in elderly patients with chronic venous insufficiency: its efficacy and tolerability.	Oxerutin* 900–1200 mg/day	6 months	104	Treatment was well tolerated.
Nocker [20]	A 3-month, randomized double blind dose-response study with 0-beta-hydroxyethyl-rutoside*- oral solution.	Oxerutin 600 mg, 900 mg, 1200 mg, 1500 mg	3-month	30	Digestibility was "very good" to " good" in the placebo-group and in the groups with active ingredient mostly as "good". No side effects reported.
Piller[26]	A double-blind, cross-over trial of O-(beta-hydroxyethyl)-rutosides (benzo-pyrones) in the treatment of lymphoedema of the arms and legs.	Oxerutin*‡** 3 grams/day	6 months	40	Very low incidence, and relative insignificance, of side effects. Only 2.5% of patients have mild gastro-intestinal disorders, and only in the first 2 weeks.

Renton[24]	The effect of hydroxyethylrutosides on capillary filtration in moderate venous hypertension: a double-blind study.	Oxerutin* 1000 mg/day	4 weeks	40	There were no side effects reported. Withdrawals were due to causes unrelated to treatment.
Rehn[22]	Investigation of the therapeutic equivalence of different galenical preparations of O-(beta-hydroxyethyl)-rutosides following multiple dose peroral administration.	Oxerutin 900-1000 mg	12 weeks	100 women	Safety results not reported.
Rehn[21]	Time course of the anti-oedematous effect of o-(beta-hydroxyethyl)-rutosides in healthy volunteers.	Oxerutin* 1000 mg/day	3 weeks	16	No adverse drug effects reported.
Rehn[3]	Comparison between the efficacy and tolerability of oxerutins and troxerutin in the treatment of patients with chronic venous insufficiency.	Troxerutin 900 mg/day or Oxerutin 900 mg	12 weeks	12	Both compounds were well tolerated and there were no adverse events reported with either treatment.
Steru[14]	Clinical assessment of a phlebotrope: Veinamitol Study	Oxerutin‡ 1000 mg	2 months	186	Tolerance was excellent. The only secondary effects amounted to some benign cases of digestive intolerance.
Unkauf[39]	Investigation of the efficacy of oxerutins compared to placebo in patients with chronic venous insufficiency treated with compression stockings.	Oxerutin* 1000 mg/day	12 weeks	133	No withdrawals for treatment-related adverse events. Adverse reactions in trial group similar to placebo. No treatment effects on laboratory parameters.
Wright[40]	Oxerutins in the prevention of recurrence in chronic venous ulceration: randomized controlled trial.	Oxerutin** 1000 mg/day	18 months	138	Safety results not reported.
Wadworth[18]	Hydroxyethylrutosides. A review of its pharmacology, and therapeutic efficacy in venous insufficiency and related disorders.	Oxerutin* 0.6-3 g/day	6 months	Up to 149	Well tolerated. Most reported events have been mild and similar in treatment and placebo groups.
Wijayanegara[19]	A clinical trial of hydroxyethylrutosides in the treatment of hemorrhoids of pregnancy.	Oxerutin* 1000 mg/day	2-4 weeks	97	Safe and effective. Three patients reported mild transient side effects in the active treatment group. No drug related problems in pregnancy or delivery.

***Oxerutin®** O-(beta-hydroxyethyl)-rutoside—a mixture of mono-, di-, tri-, and tetrahydroyethylrutosides
****Paroven®** 0-(beta- hydroxyethyl)-rutosides
Troxerutin 3',4',7-Tris(hydroxyethyl)rutin
Veinamatol® 3',4',7-Tris(hydroxyethyl)rutin
Venalot® 3',4',7-tris-(hydroxy-ethyl)-rutin (troxerutin) + 5.6-benzo-alpha-pyron (coumarin)
‡Venoruton ® O-(beta-hydroxyethyl)-rutosides
Zyma® 0-(beta- hydroxyethyl)-rutosides