DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date JUN 9 2000

From Deputy Director, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-800

Subject 75-Day Premarket Notification for New Dietary Ingredients

To Dockets Management Branch, HFS-305

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New Dietary Ingredient:	Troxerutin
Firm:	Nutratech Inc.
Date Received by FDA:	March 27, 2000
90-Day Date:	June 24, 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 public display in docket number 95S-0316 after June 24, 2000.

Virginia L. Wilkening

Virginia L. Wilkening

95S-0316

RPT 67

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

JUN 9 2000

Carl Germano, RD, CNS, LDN
Nutratech, Incorporated
East Coast Office
208 Passaic Avenue
Fairfield, New Jersey 07004

Dear Mr. Germano:

This is in response to your letter to the Food and Drug Administration (FDA) dated March 27, 2000, making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)). Your letter notified FDA of the intent of Nutratech, Inc. to market a dietary supplement containing a new dietary ingredient, troxerutin.

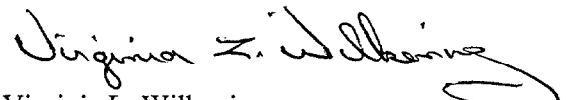
21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing troxerutin will reasonably be expected to be safe. Your submission consisted of 27 published studies of rutosides, a summary of those studies, and a collection of English- and foreign-language web documents describing sales of troxerutin and related rutosides in other countries. Of the 27 studies you included in your submission, only four studies specifically examined troxerutin and are relevant to establishing whether a dietary supplement containing troxerutin would reasonably be expected to be safe[1]. The remaining studies 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, they describe the results of studies of substances that are related to troxerutin but which have different pharmacologic actions, or are not studies designed to provide data that are relevant to assessing the safety of the chronic consumption of troxerutin in a dietary supplement (for example, they are short-duration studies, describe the effects of its non-oral use, do not include clinical measurements that allow its effects to be evaluated, or use patients with underlying diseases which raise questions about their relevance to examining the effects of the substance in healthy humans).

The four studies cited above that are relevant to examining the safety of troxerutin do not provide an adequate basis to conclude that troxerutin, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. None of the studies include adequate comparative clinical chemistry, urinalysis tests, or other measurements that would be useful in evaluating the systemic consequences of the chronic use of troxerutin in healthy humans. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Please contact us if you have any questions concerning this matter.

Sincerely yours,



Virginia L. Wilkening
Deputy Director for Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

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[1]Lefebvre et al., Rev Fr Gynecol Obstet (1991), 86(2 Pt 2):206-208; Rehn et al., Arzneim-Forsch/Drugs Res (1993), 43 II, Nr 10:1060-1063; Boisseau et. al. J Cardiovasc Surg (1995), 36:369-374; Marhic, C., Rev Fr Gynecol Obstet (1991), 86 (2 Pt. 2): 209-212.

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March 20, 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

Dear Sir or Madam,

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, on its own behalf, Nutratech, Inc. wishes to notify the Food and Drug Administration that it will market a new dietary ingredient, TROXERUTIN, a naturally-occurring substance that is extracted from the flower buds of the Chinese Scholartree. Accordingly, enclosed are an original and two copies of this notification.

As a dietary supplement, TROXERUTIN will be put into a capsule, tablet, powder, or bar that will be suggested to be taken at 100 mg to 1000 mg/day orally.

Attached are a summary and reports of the safety studies and other information establishing that this dietary ingredient, when used as set forth above, is reasonably expected to be safe. These supporting studies include:

- A TROXERUTIN safety profile with references,
- Pre-clinical pharmacology and toxicology journal articles and abstracts,
- Clinical trial journal articles and abstracts,
- A selection of product information and package inserts from TROXERUTIN formulations marketed internationally.

Yours truly,

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

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TROXERUTIN (CAS 7085-55-4)

Basis for Concluding Troxerutin is Reasonably Expected to be Safe

Troxerutin* is a flavonoid derived from the natural bioflavonoid rutin, which is extracted through hydroxyethylation from flower buds of the Chinese Scholartree, *Sophora japonica L.* Troxerutin is available under many brand names throughout the world (Table 1). It is commonly used in Europe, Asia, New Zealand, Australia, and South America, both alone and in combination with other compounds, as an anticoagulant, a radioprotective agent and for the treatment of chronic venous insufficiency (CVI), varicose veins, and hemorrhoids. In the United States, troxerutin is used as a component in dietary supplement formulas. Troxerutin has been the subject of more than 100 clinical trials, animal studies, and *in vitro* studies. Clinical trials have been conducted using doses of 100 mg to 4000 mg per day orally for up to 6 months. In all trials, troxerutin has been well tolerated; only rarely have participants experienced mild transitory adverse events, such as nausea, headache, and gastrointestinal discomfort (Table 2).

SAFETY ASSESSMENTS

Mutagenesis

Although it is known that some flavonoids are mutagens, 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.[1]

***Systematic Name:** 2-(3,4-Bis(2-hydroxyethoxy)phenyl)-3-((6-O-(6-deoxy-alpha-L-manno- pyranosyl)-beta-D-glucopyranosyl)oxy)-5-hydroxy-7-(2-hydroxy ethoxy)-4H-1-benzopyran-4-one

Flavone, 3,5-dihydroxy-3',4',7-tris(2-hydroxyethoxy)-, 3-(6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranoside)

3',4',7-Tris(hydroxyethyl)rutin

Molecular Formula: $C_{33}H_{42}O_{19}$

SAFETY STUDIES IN ANIMALS

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.[2]

Preuss-Ueberschar and colleagues found no reproduction toxicological risk with Venalot® [3',4',7-tris-(hydroxy-ethyl)-rutin (troxerutin) + 5.6-benzo-alpha-pyron (coumarin)] in a combined study of 3 generations of SPF Wistar rats evaluated on the fertility and teratogenicity, as well as perinatal and postnatal 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 3 weeks pretreatment. 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.[3]

In a study conducted by Pulsford and colleagues, a 6:1 mixture of Venalot® [3',4',7-tris-(hydroxy-ethyl)-rutin (troxerutin) + 5.6-benzo-alpha-pyron (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.[4]

Venoruton® [O-(beta-hydroxyethyl)-rutoside] 20 mg per minute was infused intra-arterially into the canine forelimb perfused at constant flow during the simultaneous intra-arterial infusion of histamine 4 micrograms base/minute or bradykinin 2 micrograms per minute. The infusion of Venoruton® alone for 40 minutes resulted in a small but significant increase in forelimb arterial pressures but no change in systemic pressure or forelimb skin lymph flow, protein concentration, or protein transport. Subsequent infusion of either histamine or bradykinin resulted in a significant decrease in forelimb arterial pressures and a marked increase in skin lymph flow, lymph total protein concentration, and lymph total protein transport. The changes in forelimb vascular pressures and skin lymph parameters were similar to those seen during the infusion of either histamine or bradykinin alone. These data indicate that the intra-arterial infusion of Venoruton® at this

dosage does not inhibit the ability of simultaneously infused histamine or bradykinin to increase transvascular fluid and macromolecular efflux in the canine forelimb perfused at constant arterial inflow.[5]

CLINICAL STUDY SAFETY DATA

Troxerutin has an excellent side effect profile. Adverse events are rare and when they occur, are usually mild and transient. In Indonesia, 97 women with first-, second-, or third-degree hemorrhoids during pregnancy were given either troxerutin 1000 mg per day or placebo. Side effects were mild and transient, and there were no troxerutin-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 troxerutin 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 troxerutin treatment.[6]

A 4-week study designed by Renton and colleagues to measure the effects of hydroxyethylrutosides 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.[7] Similarly, there were no side effects experienced by 16 chronic schizophrenics who were treated for 3 months with troxerutin or a placebo in a randomized, double-blind, crossover trial.[8]

Troxerutin 900 mg per day was very well tolerated in a 6-month study of 102 patients over 65 years of age with CVI, conducted by MacLennan and colleagues. Both adverse events and laboratory measurements were comparable in the troxerutin group and placebo group. Forty-two patients reported 51 adverse events—26 in the troxerutin group and 25 in the placebo group. Adverse events resulted in withdrawal from the trial in 11 cases—3 in the troxerutin 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 troxerutin group and 79 abnormal transitions in 31 patients in the placebo group. Statistically significant variations in the troxerutin 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.[9]

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.[10] In a study conducted by Rehn and colleagues, 16 healthy volunteers took either o-(beta-hydroxyethyl)-rutosides 1000/d for 3 weeks or placebo. There were no unusual laboratory findings. GGT, GOT, GPT, creatinine, blood glucose, hemoglobin, erythrocytes, and leukocytes remained

within normal range with respect to pretreatment values following placebo and troxerutin treatment. No adverse drug effects were reported.[11] In another study, the effect of troxerutin on fibrinolysis and hemorheology was investigated in 85 patients with CVI. During the 15-day trial there were 5 withdrawals from the troxerutin group and 5 from the placebo group, all for reasons unrelated to treatment.[12]

In a double-blind comparison between the efficacy and tolerability of oxerutins and troxerutin for the treatment of CVI, 12 postmenopausal women received 900 mg per day oxerutins or troxerutin for 12 weeks. No adverse events were reported.[13] 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. In a 6-month study conducted by Piller and colleagues, patients took Venoruton® [O-(beta-hydroxyethyl)-rutoside] 3 grams per day, and 70% of participants preferred the effects of the active drug.[14]

In a multi-centre clinical trial designed to assess the efficacy and safety of 0-(beta-hydroxyethyl)-rutosides, 101 patients with post-thrombotic syndrome took troxerutin 300 mg 4 times daily or placebo for 8 weeks. Troxerutin was well tolerated in most patients. In the troxerutin 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 taking placebo who stopped after the 4th week.[15]

When the hematological parameters of erythrocytes, hemoglobin, thrombocytes, thrombelastogram, prothrombin time, blood-clotting, and bleeding time were examined in 20 mothers and their infants, after administration of Venalot ®, a combination of coumarin and troxerutin, all values tested were within normal ranges before and after treatment.[16]

DOSE CONSIDERATIONS

Doses for troxerutin, used as a dietary supplement, were calculated after an assessment of animal and human clinical trial data. The usual dose for adults is 600 to 1000 mg per day twice daily with a maximum dose of 4 grams a day. Troxerutin had been given in clinical trial for 6 months.[9] Marhic and colleagues, gave a dose of 4 grams daily without clinical consequence to women at least 4 months pregnant.[17]

The effect of 3 different oral doses of Venoruton® [O-(beta-hydroxyethyl)-rutoside; HR] on the skin capillary resistance of Sprague-Dawley rats aged 8 to 10 weeks, 6 months or 1 year was investigated by Gabor and colleagues. The capillary resistance was measured over a period of 24 hours after a single dose. The results were compared with another group aged 6 months who received HR intraperitoneally (IP). In most cases, a significant effect could be seen in 2 to 4 hours, persisting until at least 8 hours and in some cases 24 hours. When comparative data were gathered on the hydroxyethyl components tetra-HR, tri-HR, di-HR, and mono-7-HR, the most active was mono-7-HR.[18]

PHARMACOLOGY

Uptake

Nine patients undergoing surgical treatment of varicosity were enrolled in a study exploring troxerutin uptake by the long saphenous vein. Troxerutin showed 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.[19]

Elimination

The major route of hydroxyethylrutoside excretion in both animals and humans is via the biliary-enteric route. When [14C]-hydroxyethylrutoside (Venoruton®) was administered orally to 3 volunteers, 3.05% to 5.97% of the [14C] was excreted in urine. Unchanged urinary [14C]- hydroxyethylrutosides represented 1.57% to 1.96% of the total dose. Significant levels of [14C] were detected in plasma within 1 hour of dosing, and peak levels were between 2 to 9 hours. Radioscanning and spectal methods detected the presence of [14C]-3',4',5,7-tetra-O-(beta- hydroxyethyl)rutoside, [14C]-3',4',7-tri-O-(beta-hydroxyethyl)rutoside and [14C]-4',7-di-O-(beta-hydroxyethyl)rutoside in urine. A second dose of [14C]- hydroxyethylrutoside following extended dosage of non-labeled hydroxyethylrutoside did not result in any increase in urinary [14C] excretion over a single oral dose.[20]

Mechanism of action

Venoruton® [O-(beta-hydroxyethyl)-rutoside] did not cause supersensitivity to either exogenous or endogenous (stimulation-released) noradrenaline, in strips of the saphenous vein of the dog. It did cause a significant blockade of the inactivation of noradrenaline, in oil immersion experiments. In incubation experiments with 3H-isoprenaline, Venoruton (100 to 900 mumol/l) caused a dose-dependent inhibition of O-methylation; and had additive effects with the COMT inhibitor U-0521. In incubation experiments with 3H- adrenaline, formation of metanephrine was inhibited, neuronal uptake and oxidative deamination remaining unaffected. After intravenous administration of HR (100 mg/kg), the O-methylating capacity of blood vessels was similarly reduced. Investigators concluded that HR affected exclusively the extraneuronal O-methylating system (probably both by inhibiting COMT and depressing uptake).[21]

Troxerutin may have antithrombotic action. In an experimental model of thrombosis, troxerutin 10 mg/kg markedly inhibited thrombus formation in venules, and troxerutin 50 mg/kg in arterioles. The antithrombotic effect lasted for ~7.5 hours with 100 mg/kg in venules and ~5 hours in arterioles. *In vitro*, troxerutin had no effect on coagulation parameters. In concentrations of 100 micrograms/ml in platelet rich plasma, troxerutin significantly inhibited platelet adhesion to the extracellular matrix and siliconised glass, as well as platelet spreading.[22] The effect of Venoruton® [O-(beta-hydroxyethyl)-rutoside] on the activity of factor XIII in rat plasma was studied *in vivo*. Animals were subjected to intragastric administration of the drug 6 times a week for 90 days in doses of 5 mg/100 g body weight. There was an approximate 2-fold increase in factor XIII activity beginning after several days of treatment and lasting for several weeks. Then an attenuation of factor XIII activity down to the control level took place in spite of systematic Venoruton administration.[23]

Table 2.

Troxerutin Safety Results

	Author	Title of study	Dose range	Duration	Patients	Safety Results
1	Wijayanegara [6]	A clinical trial of hydroxyethylrutosides in the treatment of haemorrhoids of pregnancy.	Venoruton 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 the pregnancy or delivery.
2	Renton [7]	The effect of hydroxyethylrutosides on capillary filtration in moderate venous hypertension: a double-blind study.	Venoruton 1000 mg/day	4 weeks	40	There were no side effects. The dropouts were due to causes unrelated to treatment.
3	Casley-Smith [8]	Benzo-pyrones in the treatment of chronic schizophrenic diseases.	Venoruton	3 months	16	No side effects with the active substance.
4	MacLennan [9]	Hydroxyethylrutosides in elderly patients with chronic venous insufficiency: its efficacy and tolerability.	HR 900–1200 mg/day	6 months	104	Well tolerated.
5	Lefebvre [10]	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.
6	Rehn [11]	Time course of the anti-oedematous effect of o-(beta-hydroxyethyl)-rutosides in healthy volnteers.	HR 1000/day	3 weeks	15	No adverse drug effects.
7	Boisseau [12]	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.
8	Rehn [13]	Comparison between the efficacy and tolerability of oxerutins and troxerutin in the treatment of patients with chronic venous insufficiency.	Troxerutin 900 mg/day	12 weeks	12	No adverse effects.
9	Piller [14]	A double-blind, cross-over trial of O-(beta-hydroxyethyl)-rutosides (benzo-pyrones) in the treatment of lymphoedema of the arms and legs.	HR 3 grams/day	6 months	26	70% of patients preferred the active compound to placebo.
10	de Jongste [15]	A double blind three center clinical trial on the short-term efficacy of 0-(beta-hydroxyethyl)-rutosides in patients with post-thrombotic syndrome.	HR capsules 1200 mg/day	8 weeks	41	Mild side effects.
11	Krajnovic [16]	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.
12	Marhic [17]	Clinical and rheological efficacy of troxerutin in obstetric gynecology.	Troxerutin 4 grams/day	4 months	60	Excellent acceptability and tolerance.

	Author	Title of study	Dose range	Duration	Patients	Safety Results
13	Belcaro [24]	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.	Venoruton 3000 mg/day	2 weeks	12	Not reported.
14	Krajnovic [16]	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.
15	Lukjan [25]	The effect of HR (O-Beta-Hydroxyethylo-Rutoside, Venoruton) on the deformability of erythrocytes in patients with arteriosclerosis obliterans of lower limbs.	Venoruton IV 1000 mg/day	3 weeks	44	Not reported.
16	Unkauf [26]	Investigation of the efficacy of oxerutins compared to placebo in patients with chronic venous insufficiency treated with compression stockings.	Venoruton 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.
17	Wright [27]	Oxerutins in the prevention of recurrence in chronic venous ulceration: randomized controlled trial.	Paroven 1000 mg/day	18 months	138	Not reported.

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

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