



September 12, 2007

Mary K. Engle
Associate Director
Division of Advertising Practices
Federal Trade Commission
600 Pennsylvania Avenue, N.W.,
Washington, D.C. 20580

Barbara Schneeman, Ph.D.
Director, Office of Nutritional Products, Labeling, and Dietary Supplements
Food and Drug Administration
5100 Paint Branch Parkway
College Park MD 20740-3835

Dear Sir or Madam,

The Center for Science in the Public Interest requests the Federal Trade Commission to halt unfair and deceptive advertising by Natrol for its Promensil dietary supplement. Such advertising violates section 5 of the Federal Trade Commission Act, 15 USC Sec. 45.

The Center for Science in the Public Interest also requests the Food and Drug Administration to halt the unsubstantiated statements of nutritional support by Novogen Inc. on the Promensil package label. These unsubstantiated statements violate section 403(r)(6)(B) of the Federal Food, Drug and Cosmetic Act.

Promensil is a brand of red clover dietary supplement manufactured by Novogen of Australia.¹ Natrol of Chatsworth, California, obtained the rights in 2006 to sell Promensil in the United States.²

During the spring of 2007, Natrol advertised Promensil in Health³ and Alternative Medicine⁴ magazines, claiming that:

“22 clinical studies can’t be wrong. Promensil provides more than relief from hot flashes! Promensil is a natural alternative for menopause that is clinically proven

¹ <http://www.novogen.com/> (accessed September 4, 2007)

² <http://www.natrol.com/pr2006/061023/> (accessed September 4, 2007)

³ <http://www.health.com/health/> (accessed September 4, 2007)

⁴ <http://www.alternativemedicine.com/> (accessed September 4, 2007)

to safely relieve hot flashes, night sweats, sleep disturbances and mood swings while promoting breast health, heart health and emotional well-being.”

“If you are experiencing menopause symptoms, don’t suffer any longer, get Promensil today and get back in control of your days and your nights.” (See Attachment 1 for a copy of this ad.)

The product’s label claims that Promensil is “clinically proven,” “Natural relief for menopausal symptoms and more,” and “relieves hot flashes,” “relieves night sweats,” promotes breast health,” and “promotes heart health.” (See Attachment 2 for a copy of the label.)

The 22 studies mentioned in the ad are not listed on the websites of Natrol⁵ or of Promensil.⁶ In response to our inquiry, Natrol emailed us their list of 22 allegedly “can’t be wrong” clinical studies.⁷ [See Attachment 3. These 22 studies will be referred to hereafter by their individual numbers, (1) through (22).]

This list of 22 studies does not support the claims Natrol makes for Promensil in its advertisement. In fact, the ad grossly misrepresents the scientific research on Promensil and is unfair and deceptive.

There are only 17 –not 22-- clinical studies on Natrol’s list

Natrol counted one study three times, another study twice. Studies (1), (2), and (5) are all the same study in British women. Studies (15) and (18) are the same study in Ecuadoran women. Just because the authors of the two studies chose to write up their results in several scientific reports doesn’t turn them into five different studies.

In addition, studies (10) and (20) are pharmacokinetic studies tracing the digestion, absorption, and metabolism of red clover supplements. Neither looked for nor found any benefits from Promensil, so they don’t belong on a list of studies supposedly demonstrating clinical benefits.

Natrol’s “can’t be wrong” studies do not demonstrate that Promensil provides relief from hot flashes

The totality of the evidence does not support this claim.

Five of the studies tested the effect of Promensil on hot flashes. Three of the five, including the largest two and the longest one, found the supplement ineffective for reducing the average number of daily hot flashes. Promensil did not lessen the frequency of hot flashes in 86 British women (1), 23 Australian women (7), or

⁵ <http://www.natrol.com/> (accessed September 4, 2007)

⁶ <http://www.promensil.com/us/> (accessed September 4, 2007)

⁷ Email from Natrol to CSPI, June 15, 2007.

84 U.S. women (12). Two small trials of 15 Peruvian women (4) and of 15 Dutch women (16) found that Promensil reduced the average number of daily hot flashes from 7 to 4 and 5 to 4, respectively, after two to four months.

Natrol’s “can’t be wrong” studies do not demonstrate that Promensil “is a natural alternative for menopause.”

The totality of the evidence does not support this claim.

Five of the studies tested the effect of Promensil on overall menopausal symptoms. Four of the five, including the largest two and the longest one, found the supplement ineffective for lessening the severity of menopausal symptoms, as measured by the widely used Greene Climacteric Scale. This Scale tracks the severity of psychological, physical, and vasomotor symptoms. Promensil did not relieve menopausal symptoms in 86 British women (1), 23 Australian women (7), 84 U.S. women (12), or 15 Dutch women (16). The one Promensil trial that detected an effect on symptoms, a small trial of 15 middle-class Peruvian women, provided no details about the scale used (4). A sixth trial using a different red clover product called Menoflavon and employing an older menopausal symptom scale called the Kupperman index found that two tablets a day for 3 months improved symptoms in 53 Ecuadoran women (18).

Natrol’s “can’t be wrong” studies do not demonstrate that Promensil promotes “heart health.”

The totality of the evidence does not support this claim. Of the established risk factors for heart disease:⁸

Total cholesterol

Eight studies (2, 8, 9, 11, 13, 17, 18, 22) found no effect of Promensil on total cholesterol. One unpublished study found that Promensil lowered total cholesterol in postmenopausal Peruvian women (3).

LDL cholesterol

Six studies (2, 8, 9, 11, 13, 18) found no effect of Promensil on LDL levels.

HDL cholesterol

Four studies (2, 8, 9, 11) found no effect of Promensil on HDL levels. One study (7) found that HDL rose with 40 mg of Promensil but not with 160 mg a day, suggesting that the change at 40 mg was just random variation. Another study (17) found that HDL levels rose in postmenopausal but not in premenopausal women.

⁸ <http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf>

Blood pressure

Five studies (2, 9, 18, 21, 22) found no effect of Promensil on blood pressure. One study (11) found an effect of Promensil on daytime blood pressure but not on overall 24-hour blood pressure.

Of emerging risk factors for heart disease:⁹

Triglycerides

Five studies (2, 8, 9, 11, 17) found no effect of Promensil on triglycerides levels. One study (18) found a decrease.

Of other markers not currently recognized as risk factors for heart disease:

Promensil improved arterial compliance in 17 postmenopausal women (8) and arterial stiffness in 34 postmenopausal women (21). These observations need to be confirmed in larger studies.

Natrol’s “can’t be wrong” studies do not demonstrate that Promensil promotes “breast health,” except possibly in those suffering from a specific condition called cyclical mastalgia.

Promensil reduced the “breast pain score” in five women with cyclical mastalgia who took 40 mg/d, but not in seven other women with mastalgia who took 80 mg/d (6). Nine of 12 women with mastalgia and taking Promensil reported more than a 25% decrease in pain compared to two of the six who received a placebo. One small study does not provide sufficient basis for a definitive statement regarding breast health.

Conclusion

Natrol’s claim that there is a substantial and unanimous body of scientific evidence demonstrating the efficacy of Promensil for women is not supported by the totality of the scientific evidence cited by the company.

On the contrary, Natrol’s inflated list of 22 clinical studies that allegedly “can’t be wrong” reveals mostly contradictory and inconclusive research.

This contradictory and inconclusive research is the reason why authorities ranging from the federal government’s National Center for Complementary and Alternative Medicine (NCCAM) which funds research on red clover,¹⁰ to the Internet’s Natural Pharmacy (a compendium of dietary supplement

⁹ <http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf>

¹⁰ <http://nccam.nih.gov/health/redclover/> (accessed September 4, 2007)

monographs),¹¹ and the pro-industry Healthnotes encyclopedia (which merchants use to encourage their customers to buy dietary supplements),¹² describe the scientific evidence for red clover with terms such as “mixed,” “no beneficial effects,” “not enough,” “inconsistent,” “weak,” and “contradictory, insufficient, or preliminary.”

Natrol, by grossly misrepresenting this research to make it look otherwise, has deceived and bilked consumers and should be required to reimburse those consumers, run corrective advertising to set the record straight, and pay a fine.

Respectfully submitted,



David Schardt
Senior Nutritionist



Stephen Gardner
Director of Litigation

¹¹ <http://healthlibrary.epnet.com/GetContent.aspx?token=e0498803-7f62-4563-8d47-5fe33da65dd4&chunkid=21854> (accessed September 4, 2007)

¹² <http://www.netrition.com/cgi/healthnotes.cgi?ContentID=2153008> (accessed September 4, 2007)

Attachment 1: Promensil ad

Why
promensil.?

...22 clinical
studies can't
be wrong.

Balance Your Hormones,
Stay In Control*

- Relieves hot flashes*
- Relieves night sweats*
- Promotes breast health*
- Promotes heart health*

CLINICALLY
PROVEN & DOCTOR
RECOMMENDED

promensil.

Natural relief
for menopausal
symptoms*
and more



30 TABLETS 60 mg each

* A dietary supplement of
plant estrogens extracted
from red clover.

Promensil®
provides more than
relief from hot flashes!

Promensil® is a natural alternative for menopause that is clinically proven to safely relieve hot flashes, night sweats, sleep disturbances and mood swings while promoting breast health, heart health and emotional well-being.†

Promensil tablets are standardized to contain 40mg of isoflavones extracted from red clover, one of the richest natural sources of isoflavones, in a unique ratio to maximize its effectiveness.

If you are experiencing menopause symptoms, don't suffer any longer, get Promensil today and get back in control of your days and your nights.

Questions? Call 877.417.7663.
Coupon available at www.promensilusa.com.

Available at fine health food stores, supercenters, Walgreens, CVS, Rite Aid, Meijer, and everywhere dietary supplements are sold.

NATROL

©2007 Natrol, Inc.
Natrol, Inc. is the exclusive distributor
of Promensil® products in the U.S.A.

† These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

Attachment 2: Promensil label

NOVOGEN

**Balance Your Hormones,
Stay In Control***

- Relieves hot flashes*
- Relieves night sweats*
- Promotes breast health*
- Promotes heart health*

**CLINICALLY
PROVEN & DOCTOR
RECOMMENDED**

promensil®

**Natural relief
for menopausal
symptoms*
and more**



30 TABLETS one daily

A dietary supplement of
plant estrogens extracted
from red clover

Why do women around the world use Promensil?
Clinical research has shown that in cultures consuming a natural diet abundant in isoflavones women have fewer and milder menopausal symptoms. Promensil's active ingredients are Red Clover isoflavones, which complement the body's declining estrogen levels around menopause*, so relieving menopausal symptoms* and promoting breast health* and heart health*. Independent research has proven Promensil to be the only product to contain the amount of isoflavones claimed on the package.

<p>Relieves</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Hot flashes* <input checked="" type="checkbox"/> Night sweats* <p>Promotes</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Breast health* <input checked="" type="checkbox"/> Heart health* <input checked="" type="checkbox"/> Emotional well being* <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Does not cause weight gain* <input checked="" type="checkbox"/> Restores hormone balance* 	<p>Supplement Facts</p> <p>Serving size 1 tablet Servings per container 30</p> <hr/> <p>Amount per tablet:</p> <p>Isoflavones as Red Clover Extract 40 mg**</p> <hr/> <p>Each tablet contains the equivalent of 57mg of isoflavones in glycoside form.</p> <p>** Daily value not established</p>
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Ingredients
Red clover isoflavone extract, Dicalcium phosphate, Microcrystalline cellulose, Hypromellose, Magnesium stearate, Mixed tocopherols, Silica, Soy polysaccharide, Titanium dioxide color, Polyethylene glycol, FD&C Red #40, Yellow #6, Yellow #5 and Blue #1.

Directions for use
One daily with a meal.

Not recommended for pregnant women or children under the age of 15.
Store in a cool dry place below 85°F

Promensil customer care

- Toll free**
1 877 417 7663
- www.promensil.com**

Distributed in USA by
Novogen Inc, 1177 Summer Street,
Stamford, CT 06905

US Patents: 6,562,380; 6,642,212;
6,987,098.

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease. The FDA does not review any dietary supplement claims for accuracy.

NOVOGEN
the world leader in isoflavone research

Attachment 3: Natrol's list of 22 clinical studies

1. Atkinson C, Warren RM, Sala E, et al. Red-clover-derived isoflavones and mammographic breast density: a double-blind, randomized, placebo-controlled trial [ISRCTN42940165]. *Breast Cancer Res.* 2004;6:R170-R179. [PMID [15084240](#)]
2. Atkinson C, Oosthuizen W, Scollen S, Loktionov A, Day NE, Bingham SA. Modest protective effects of isoflavones from a red clover-derived dietary supplement on cardiovascular disease risk factors in perimenopausal women, and evidence of an interaction with ApoE genotype in 49-65 year-old women. *J Nutr.* 2004;134:1759-1764. [PMID [15226466](#)]
3. Jeri A. Effects of isoflavone phytoestrogens on lipid profile in postmenopausal Peruvian women. Paper presented at: 10th World Congress on the Menopause; 2002; Berlin, Germany.
4. Jeri A. The use of an isoflavone supplement to relieve hot flushes. *Female Patient.* 2002;27:35-37. [PMID Not Indexed]
5. Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA. The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr.* 2004;79:326-333. [PMID [14749241](#)]
6. Ingram DM, Hickling C, West L, Mahe LJ, Dunbar PM. A double-blind randomized controlled trial of isoflavones in the treatment of cyclical mastalgia. *Breast.* 2002;11:170-174. [PMID [14965665](#)]
7. Knight DC, Howes JB, Eden JA. The effect of Promensil, an isoflavone extract, on menopausal symptoms. *Climacteric.* 1999;2:79-84. [PMID [11910671](#)]
8. Nestel PJ, Pomeroy S, Kay S, et al. Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. *J Clin Endocrinol Metab.* 1999;84:895-898. [PMID [10084567](#)] Erratum in: *J Clin Endocrinol Metab.* 1999;84:3647.
9. Howes JB, Sullivan D, Lai N, et al. The effects of dietary supplementation with isoflavones from red clover on the lipoprotein profiles of post menopausal women with mild to moderate hypercholesterolaemia. *Atherosclerosis.* 2000;152:143-147. [PMID [10996349](#)]
10. Setchell KD, Brown NM, Desai P, et al. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. *J Nutr.* 2001;131(suppl 4):1362S-1375S. [PMID [11285356](#)]
11. Howes JB, Tran D, Brillante D, Howes LG. Effects of dietary supplementation with isoflavones from red clover on ambulatory blood pressure and endothelial function in postmenopausal type 2 diabetes. *Diabetes Obes Metab.* 2003;5:325-332. [PMID [12940870](#)]
12. Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study: a randomized controlled trial. *JAMA.* 2003;290:207-214. [PMID [12851275](#)]
13. Knudson Schult T, Ensrud KE, Blackwell T, Ettinger B, Wallace R, Tice JA. Effect of isoflavones on lipids and bone turnover markers in menopausal women. *Maturitas.* 2004;48:209-218. [PMID [15207886](#)]
14. Imhof M, Gocan A, Reithmayr F, et al. Effects of a red clover extract (MF11RCE) on endometrium and sex hormones in postmenopausal women. *Maturitas.* 2006;55:76-81. [PMID [16513301](#)]

15. Chedraui P, Hidalgo L, San Miguel G, Morocho N, Ross S. Red clover extract (MF11RCE) supplementation and postmenopausal vaginal and sexual health. *Int J Gynaecol Obstet.* 2006;95:296-297. [PMID [17007858](#)]
16. van de Weijer PH, Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. *Maturitas.* 2002;42:187-193. [PMID [12161042](#)]
17. Campbell MJ, Woodside JV, Honour JW, Morton MS, Leathem AJ. Effect of red clover-derived isoflavone supplementation on insulin-like growth factor, lipid and antioxidant status in healthy female volunteers: a pilot study. *Eur J Clin Nutr.* 2004;58:173-173. [PMID [14679383](#)]
18. Hidalgo LA, Chedraui PA, Morocho N, Ross S, San Miguel G. The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: a randomized, double-blind, placebo-controlled study. *Gynecol Endocrinol.* 2005;21:257-264. [PMID [16373244](#)]
19. Woods R, Colville N, Blazquez J, Cooper A, Whitehead MI. Effects of red clover isoflavones (Promensil) versus placebo on uterine endometrium, vaginal maturation index and the uterine artery in healthy postmenopausal women. Paper presented at: Annual Meeting of the British Menopause Society; July 3-4, 2003; Manchester, England.
20. Howes J, Waring M, Huang L, Howes LG. Long-term pharmacokinetics of an extract of isoflavones from red clover (*Trifolium pratense*). *J Altern Complement Med.* 2002;8:135-142. [PMID [12006121](#)]
21. Teede HJ, McGrath BP, DeSilva L, Cehun M, Fassoulakis A, Nestel PJ. Isoflavones reduce arterial stiffness: a placebo-controlled study in men and postmenopausal women. *Arterioscler Thromb Vasc Biol.* 2003;23:1066-1071. [PMID [12714433](#)]
22. Howes JB, Bray K, Lorenz L, Smerdely P, Howes LG. The effects of dietary supplementation with isoflavones from red clover on cognitive function in postmenopausal women. *Climacteric.* 2004;7:70-77. [PMID: [15259285](#)]