



*promensil*®



Novogen Limited is an Australian biotechnology company dedicated to the research and development of isoflavone and isoflavonoid products and drugs. Over the past fifteen years, Novogen has conducted the largest and most comprehensive isoflavone clinical testing programs in the world.

Novogen Consumer Healthcare and our brands and products are committed to helping to regenerate customer's precious lives.



*promensil.*



## REFERENCES

- 1 Kimira M, Arai Y, Shimos K & Watanbe S. Japanese intake of Flavonoids and Isoflavonoids from foods. *J Epidemiol* 1998; 8(3): 168-75.
- 2 Couse JF, Lindzey J, G Randien K, Gustafsson JA, Korach KS. Tissue Distribution and Quantitative analysis of Estrogen Receptor Alpha and Estrogen Receptor Beta. *Endocrinol* 1997; 138(11): 64613-21.
- 3 Collins BM, Mclachlan JA, Arnold SF. The Estrogenic and Anti Estrogenic Activities of Phyto Chemicals with the human Estrogen Receptor expressed in Yeast. *Steroids* 1997; 62(4): 363-72.
- 4 Price PR, Fenwick GR. Naturally occurring oestrogens in foods - A review. *Food Addit Contam* 1985; 2(2):73-106.
- 5 Van de Weijer PHM, Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. *Maturitas* 2002, 42:187-193.
- 6 Jeri AR. The use of an isoflavones supplement to relieve hot flushes. *The female Patient* 2002; 27:35-37.
- 7 Hildalgo LA, Chedraui PA, Morocho N, Ross S, Miguel GS. The effect of red clover isoflavones on menopausal symptoms, lipid and vaginal cytology in menopausal women: A randomised, double-blind, placebo-controlled study. *Gynecological Endocrinology* 2005; 21(5):257-264.
- 8 Nachtigall LB, Fenichel R, La Grega L, Wei Lee W, Nachtigall L. The effect of isoflavone derived from red clover on vasomotor symptoms, endometrial thickness, and reproductive hormone concentrations in menopausal women. 81st Annual Meeting of the Endocrine Society. The Endocrine Society 1999.
- 9 Howes LG, Howes JB, Knight DC. Isoflavone therapy for menopausal flushes: A systematic review and meta-analysis. *Maturitas* 2006; 55(3):203-11.
- 10 Thompson Coon J, Pittler MH, Ernst E. Trifolium pratense isoflavones in the treatment of menopausal hot flushes: A systematic review and meta-analysis. *Phytomedicine* 2007; 14:153-159.
- 11 Nestel PJ, Pomeroy S, Kay S, Komesaroff P, Behrsing J, Cameron JD, West L. Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. *J Clin Endo Metab* 1999; 84(3):895-898.
- 12 Teeede 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(6):1066-71.
- 13 Jeri A. Effects of isoflavone phytoestrogens on lipid profile in postmenopausal Peruvian women. 10th World Congress on the Menopause 2002. Berlin, Germany
- 14 Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA. The effects of phytoestrogen isoflavones on bone density in women: a double blind, randomised, placebo-controlled trial. *Am J Clin Nutr* 2004; 79:326-33.
- 15 Clifton-Bligh PB, Baber RJ, Fulcher GR, Nery ML, Moreton T. The effect of isoflavones extracted from red clover (Rismostil) on lipid and bone metabolism. *J North Amer Meno Society*, 2001, 8(4):259-265.
- 16 Ingram DM, Hickling C, West L, Mahe L.J, Dunbar PM. A double blind randomised controlled trial of isoflavones in the treatment of cyclical mastalgia *The Breast* 2001.
- 17 Atkinson C, Waren RML, Sala E, Dowsett M, Dunning AM, Healey CS, Runswick S, Day NE, Bingham SA. Red clover derived isoflavones and mammographic breast density: a double blind, randomised, placebo-controlled trial. *Br Cancer Res* 2004; 6(3):R170- R179.
- 18 Powles TJ, Howell A, Gareth Evans D, McCloskey EV, Ashley S, Greenhalgh R, Affen J, Flook LA, Tidy A. Red clover isoflavones are safe and well tolerated in women with a family history of breast cancer. *Meno Inter* 2008; 14:6-12.
- 19 Powles TJ, Howell A, Gareth Evans D, McCloskey EV, Ashley S, Greenhalgh R, Affen J, Flook LA, Tidy A. Red clover isoflavones are safe and well tolerated in women with a family history of breast cancer. *Meno Inter* 2008; 14:6-12.
- 20 Woods R, Colville N, Blazquez, 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. *Brist Meno Annual Conference Manchester, UK* 2003
- 21 Hale GE, Hughes CL, Robboy SJ, Agarwal SK and Bievre M. A double-blind randomized study on the effects of red clover isoflavones on the endometrium. *Menopause* 2001; 8(5):338-46
- 22 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 health postmenopausal women. *Journal of the British Menopause Society* 2003; 52:23
- 23 Baber R, Moreton T, Kelly G and West L. Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in Women. *Climacteric* 1999; 2:85-92
- 24 Nachtigall LE, Baber RJ, Barentsen R, Durand N, Panay N, Pitkin J, van de Weijer P HM, Wysocki S. Complementary and hormonal therapy for vasomotor symptom relief: a conservative clinical approach. *J Obster and Gynecology* 2006, 279-289

## Index

## What is Promensil

## Vasomotor Symptom Relief

## Cardiovascular Support

## Bone Support

## Safety

## Menopause Treatment Algorithm

## Promensil Range





## Novogen Consumer Healthcare Standards

Novogen Consumer Healthcare Standards embodies five key attributes that ensure high quality products.

The five attributes are:

- **API –**

The Active Pharmaceutical Ingredients are sourced from GMP licensed facilities.

- **GMP –**

All products are manufactured in Good Manufacturing Practice licensed facilities to ensure the highest quality production and packaging.

- **ICH –**

Extensive Stability Studies are undertaken on all products adhering to International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) guidelines.

- **Standardisation –**

All products are standardised to guarantee every tablet delivers the same level of active ingredient.

- **Clinical Evidence –**

Fact based evidence to support efficacy and safety claims.

## Clinical Summary

Promensil was first introduced in Australia in 1997. It was one of the first natural products to help relieve symptoms of menopause. Promensil is now available in more than 16 countries and has become one of the most clinically tested natural products for women's health.

The Promensil Clinical Summary is a compilation of the trials that evaluate the efficacy and safety of the Promensil Range of women's health products.

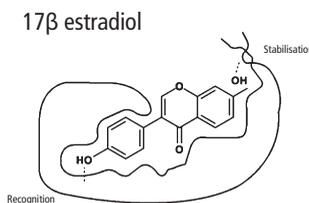
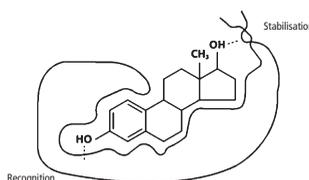
## What is Promensil?

Epidemiological studies have shown that high incidence of "Western diseases" such as cardiovascular disease, osteoporosis and menopausal symptoms are inversely related to consumption of phytoestrogens or isoflavones. In Japan, where there are significantly lower levels of "Western diseases", the normal diet provides an isoflavone intake of approximately 40mg per day<sup>1</sup>. By contrast the "Western diet" delivers 2 to 5mg of isoflavones per day.

Promensil has been developed from original research conducted by the Australian company, Novogen. Novogen research identified red clover as the best source of isoflavones and subsequently developed the standardised red clover isoflavone based product, Promensil.

## Mode of Action

Red clover isoflavones are a naturally occurring molecule with a chemical structure similar to that of steroidal estrogens. Isoflavones mimic the human bodies' natural estrogen. As a result, red clover isoflavones interact with the human estrogen receptor. Red clover isoflavones preferentially activate the beta estrogen receptors found in the brain, bones and cardiovascular system. Red clover isoflavones show very little activity in the alpha estrogen receptors found in breast and uterine tissue<sup>2</sup>.



Isoflavone

The above schematic shows the interaction of isoflavones and the human estrogen receptor.<sup>3,4</sup>

## What does Promensil Do?

Promensil Menopause has the ability to reduce the frequency and severity of hot flushes and night sweats, helping women to manage menopause naturally.

Promensil Vitality for Post Menopause supports heart and bone health in women after menopause.

Promensil is one of the most clinically tested natural women's health products in the world. Over 1,500 women have enrolled in Promensil clinical trials.

All studies were conducted by specialists in universities and teaching hospitals using Good Clinical Practice (GCP) according to ICH guidelines and published in medical peer reviewed journals.

# Vasomotor Symptom Relief

Three randomised, double blind placebo-controlled studies evaluating the use of red clover isoflavones in the treatment of vasomotor symptoms have been published. In addition two open-label trials and two Meta Analyses have also been conducted and published.

**- Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo, Van de Weijer PHM, et al. Maturitas (2002)**<sup>4</sup>

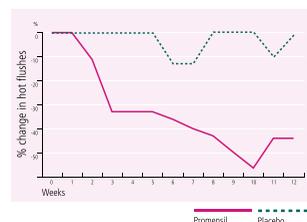
**Objectives:** To investigate the effectiveness and safety of a red clover isoflavone dietary supplement (Promensil) versus placebo on the change in hot flush frequency in postmenopausal women.

**Method:** Randomized, double blind, placebo-controlled trial 30 women with more than 12 months amenorrhoea and experiencing more than five flushes per day were enrolled. All received single blind placebo tablets for 4 weeks and were subsequently randomized to either placebo or 80mg isoflavones for a further 12 weeks. Efficacy was measured by the decrease in number of hot flushes per day and changes in Greene Climacteric Scale Score.

**Results:** During the first 4 weeks of placebo the frequency of hot flushes decreased by 16%. During the subsequent double blind phase a further, statistically significant

decrease of 44% was seen in isoflavones group ( $P < 0.01$ ), whereas no further education occurred within the placebo group. The Greene score decreased in the active group by 13% and remained unchanged in the placebo group.

**Conclusion:** Treatment with 80mg isoflavones (Promensil) per day resulted in a significant reduction in hot flushes from baseline. At the end of the study there was a significant decrease in hot flushes of 44% between the active and placebo group, demonstrating the effectiveness of Promensil in the management of hot flushes.



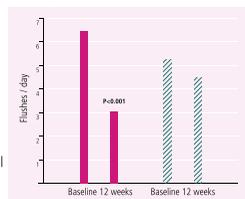
**- The Use of an Isoflavone Supplement to Relieve Hot Flushes, Jeri AR, The Female Patient (2002)**<sup>5</sup>

**Objectives:** Most studies of dietary isoflavones have focused on soy legumes (ie, soybeans), which contain genistein and daidzein—only two of the isoflavones known to have significant estrogenic properties. Red clover (*Trifolium pratense*), also a legume, contain these compounds plus two additional isoflavones, Formononetin and biochanin, which have been shown to bind to estrogen receptors to produce estrogen-like effects. This study was undertaken to evaluate the effectiveness of Promensil™, an isoflavone supplement derived from red clover, in relieving the frequency and severity of hot flushes in postmenopausal women.

**Method:** This 16-week, randomized, double-blind prospective study selected 30 healthy, non-vegetarian women who had been postmenopausal for more than 1 year, using nonprobabilistic sampling and randomly dividing them into two groups of 15. Eligibility criteria required that subjects be younger than age 60, have follicle stimulating hormone (FSH) levels of more than 30 mIU/mL, experience at least five hot flushes daily (averaged for more than 1 week), and not use HRT, antidepressants or other medications, or soy or other estrogen-active plant products for the previous 16 weeks. The median age was 52 + 0.7 years for the treatment group, and 51 + 0.8 years for the control group.

**Results:** At the end of the 16-week study, a reduction in both frequency and severity of hot flushes was reported by women in the treatment group (Promensil). The treatment group reported a statistically significant reduction of 48.5% in the frequency of hot flushes per day compared with 10.5% for the control group. There was also a reduction in the severity index for the Promensil group with a statistically significant reduction from 2.53 to 1.33 (47% reduction) and no change in the placebo group.

**Conclusion.** Based on the efficacy in hot-flush reduction reported here and findings of improved cardiovascular function, bone density, and safety reported elsewhere red-clover isoflavone supplementation offers a useful alternative for women seeking relief from acute symptoms of menopause.



**- The effects of red clover isoflavones on menopausal symptoms, lipid and vaginal cytology in menopausal women: a randomised, double-blind, placebo-controlled study, Hildago et al. Gynecological Endocrinology (2005)**<sup>6</sup>

**Background:** The unexpected results of the Women's Health Initiative study have decreased the use of conventional hormone therapy (HT), changing physicians' and patients' attitudes towards HT and increasing their interest in alternative options.

**Objective:** The present study aimed to evaluate the effect of isoflavones contained in red clover extracts (*Trifolium pratense*) on menopausal symptoms, lipids and vaginal cytology in menopausal women.

**Method:** Sixty postmenopausal women aged >40 years, non-users of HT, with Kupperman index score 15, were double-blindly randomized to receive either a commercially available red clover isoflavone supplement (80 mg/day) or placebo for 90 days. Subsequently, after a 7-day washout period, subjects switched to receive the opposite treatment for a further 90 days. Kupperman index score was determined and fasting blood and vaginal cytologic sampling performed at baseline, 90 and 180 days.

**Results:** Fifty-three women (88.3%) completed the trial. Mean age was 51.3 +/- 3.5 years, 69.7% of the women were aged 50 years or more. There was no significant effect on body mass index, weight or blood pressure after either treatment phase. Baseline Kupperman index score decreased significantly after each treatment phase, with the decrease more pronounced after the isoflavone phase (baseline: 27.2 +/- 7.7; after

isoflavone: 5.9 +/- 3.9; after placebo: 20.9 +/- 5.3,  $p < 0.05$ ). Red clover isoflavone supplementation significantly decreased the rate of menopausal symptoms and had a positive effect on vaginal cytology as expressed by improvement in karyopyknotic, cornification and basal cell maturation indices. Mean total cholesterol, low-density lipoprotein-cholesterol and triglyceride levels also decreased; however, only the latter was significantly lower compared with placebo.

**Conclusion:** Compared with placebo, red clover isoflavone supplementation in postmenopausal women significantly decreased menopausal symptoms and had a positive effect on vaginal cytology and triglyceride levels.

**- Non Prescription Alternative to HRT Nachtigall LB et al. 81st Annual Meeting of the Endocrine Society (1999)**<sup>7</sup>

**Objective:** An open-label trial was undertaken to investigate whether Promensil (40 mg once daily) reduced menopausal symptoms.

**Method:** Twenty three Symptomatic menopausal women aged 40-65 years were selected for the study. Prior to the study, the women experienced at least five hot flushes per day when averaged over 7 days, and amenorrhoea for at least 12 months. The women were asked to record the daily occurrence and severity of menopausal symptoms according to a Greene Score questionnaire for at least 1 week prior to receiving Promensil, and for at least 8 weeks while taking the supplement. Sixteen women were enrolled into and completed the study.

**Results:** After 8 weeks, Promensil 40 mg once daily significantly decreased the severity and the number of hot flushes, as well as the severity of night sweating compared with baseline. At week 8, the average number of hot flushes decreased by 58% from 8.1 to 3.6 vasomotor flushes per day.

**- Isoflavone therapy for menopausal flushes: A systematic review and meta-analysis, Howes LG et al. Maturitas (2006)**<sup>8</sup>

**Objective:** To perform a systematic review and meta-analysis of all randomized, controlled trials of isoflavone supplementation to determine the efficacy of isoflavone therapy in reducing the number of daily menopausal flushes.

**Method:** A comprehensive search of published studies of isoflavone treatment and menopausal flushing was undertaken. Studies were selected if they were randomized, were placebo controlled, provided the number of baseline flushes, the variance in flushes and the reduction in flushes. Effects for isoflavone treatment compared to control were calculated and a meta-analysis was performed.

**Results:** Isoflavone supplementation was found to be associated with a significant reduction in flushes. The percentage reduction in flushes was significantly related to the number of baseline flushes per day and the dose of isoflavone studied.

**Conclusion:** These results suggest that isoflavone supplementation may produce a slight to modest reduction the number of daily flushes in menopausal women and that the benefit may be more apparent in women experiencing a high number of flushes per day.

- *Trifolium pratense* (red clover) isoflavones in the treatment of menopausal hot flushes: A systematic review and meta-analysis, Coon JT et al. *Phytotherapy*, (2006)<sup>10</sup>

**Objective:** To critically assess the evidence of supplements containing *Trifolium pratense* (red clover) isoflavones in the reduction of hot flush frequency in menopausal women.

**Method:** Studies were selected according to predefined inclusion and exclusion criteria. All randomized clinical trials of mono-preparations containing *T. pratense* isoflavones for treating hot flushes were included.

**Results:** The meta-analysis indicates a reduction in hot flush frequency in the active treatment group (40–82 mg daily) compared with the placebo group.

**Conclusion:** There is evidence of a marginally significant effect of *T. pratense* isoflavones for treating hot flushes in menopausal women.

## Cardiovascular Support

- Isoflavones from Red Clover Improve Systemic Arterial Compliance But Not Plasma Lipids in Menopausal Women, Nestel PJ et al. *J Clin Endo Metab* (1999)<sup>11</sup>

**Objective:** The possibility that the heightened cardiovascular risk associated with the menopause can be reduced by increasing dietary isoflavone intake was tested in 17 women by measuring arterial compliance, an index of the elasticity of large arteries such as the thoracic aorta.

**Method:** An initial 3- to 4-week run-in period and a 5-week placebo period were followed by two 5-week periods of active treatment with 40mg and then 80 mg isoflavones derived from red clover isoflavones in 14 and 13 women, respectively, with 3 others serving as placebo controls throughout. Arterial compliance, measured by ultrasound as a pressure (carotid artery) and volume (outflow into aorta) relationship, was determined after each period.

**Results:** Arterial compliance rose by 23% relative to that during the placebo period with the 80 mg isoflavone dose and slightly less with the 40-mg dose. In the three women receiving continuous placebo, compliance was similar to that during the run-in period for the remaining subject.

**Conclusion:** An important cardiovascular risk factor, arterial compliance, which diminishes with menopause, was significantly improved with red clover isoflavones. As diminished compliance leads to systolic hypertension and may increase left ventricular work, the findings indicate a potential new therapeutic approach for improved cardiovascular function after menopause.

- Isoflavones Reduce Arterial Stiffness. A Placebo-Controlled Study in Men and Postmenopausal Women, Teede HJ, et al. *Arterioscler Thromb Vasc Biol* (2003)<sup>12</sup>

**Objective:** To address the vascular effects of isolated isoflavones as potential contributors to the cardioprotective properties.

**Method:** In a randomized, double-blind trial, 80 healthy subjects, 46 men and 34 women, 45 to 75 years of age, received

isoflavones enriched in either biochanin or formononetin (80 mg/d) crossed over randomly with placebo in two 6-week periods. The end points were measured at baseline and after each intervention and included large artery stiffness (systemic arterial compliance and pulse wave velocity), endothelial function in conduit arteries, 24-hour ambulatory blood pressure, and total peripheral resistance.

**Results:** Isoflavone intervention significantly reduced arterial stiffness with improved systemic arterial compliance attributable to a reduction in total peripheral resistance ( $P<0.03$ ) and a corresponding reduction in central pulse wave velocity ( $P<0.02$ ) compared with placebo. Isoflavones did not affect blood pressure ( $P<0.5$ ) or flow-mediated vasodilation ( $P<0.44$ ).

**Conclusion:** In normotensive men and postmenopausal women, red clover isoflavones enriched in Formononetin reduced arterial stiffness and total vascular resistance but had no effect on blood pressure. These effects may partly explain the lower cardiovascular risk in populations eating isoflavone-rich diets.

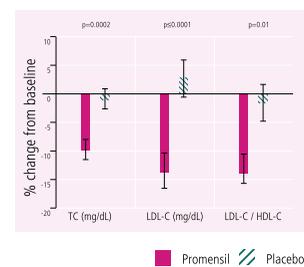
- Effects of Isoflavone Phytoestrogens on lipids in post menopausal Peruvian women. Jeri AR Abstract presented at the 10th World Congress on the Menopause, Berlin (2002)<sup>13</sup>

**Objective:** The objective of the study was to investigate the efficacy and safety of dietary isoflavones from red clover (Promensil) compared to placebo in 100 Peruvian postmenopausal women with borderline hyperlipidaemia.

**Method:** A 12 week, double-blind, randomised trial to investigate the effects of Promensil (40 mg) versus placebo on postmenopausal women with borderline hyperlipidemia. Postmenopausal women, aged <60 years with borderline hypercholesterolemia were recruited into the study. Following a 1-2 week screening period, patients who qualified at screening and baseline were randomised to either placebo or Promensil (40 mg) for 12 weeks. Women were instructed to take one tablet every morning for the entire 12 weeks.

**Results:** At baseline, for all patients total cholesterol was  $5.73 \pm 0.03$  mmol/L, HDL-C  $1.01 \pm 0.01$  mmol/L, LDL-C  $3.57 \pm 0.04$  mmol/L, triglycerides  $2.52 \pm 0.01$  mmol/L and LDL/HDL ratio was  $3.6 \pm 0.05$ . The changes in lipid parameters from baseline to 12 weeks were significantly different between groups in total cholesterol ( $-0.95 \pm 1.8\%$ ,  $-10 \pm 1.6\%$ ,  $p=0.0002$ ), LDL-C ( $2.6 \pm 3.2\%$ ,  $-13.8 \pm 2.6\%$ ,  $p<0.0001$ ) and LDL/HDL ratio ( $-1.65 \pm 3.2$ ,  $-14.28 \pm 3.3$ ,  $p=0.01$ ).

**Conclusion:** Red clover isoflavones in postmenopausal, borderline hypercholesterolaemic women resulted in significant improvements in total cholesterol, LDL-C and LDL/HDL ratio. There were no adverse effects reported.



## Bone Support

- The effects of phytoestrogen isoflavones on bone density in women: A double-blind, randomized, placebo-controlled trial, Atkinson C, et al. *Am J Clin Nutr* (2004)<sup>14</sup>

**Objective:** The objective of the study was to determine the effects on bone density of a red clover derived isoflavone supplement for 1 year.

**Method:** Women aged 49–65 yrs ( $n=205$ ) were enrolled in a double-blind, randomized, placebo-controlled trial; 177 completed the trial. Bone density, body composition, bone turnover markers and diet were measured at baseline and after 12 months.

**Results:** Loss of lumbar spine bone mineral content and bone mineral density was significantly ( $P<0.04$  and  $P<0.03$ , respectively) lower in the women taking the isoflavone supplement than those taking the placebo. There were no significant treatment effects on hip bone mineral content or bone mineral density, markers of bone resorption, or body composition, but bone formation markers were significantly increased ( $P<0.04$  and  $P<0.01$  for bone-specific alkaline phosphatase and N-propeptide of collagen type I, respectively) in the intervention group compared with placebo in postmenopausal women.

**Conclusion:** These data suggest that, through attenuation of bone loss, isoflavones have a potentially protective effect on the lumbar spine in women.

- The effect of isoflavones extracted from red clover on lipid and bone metabolism, Clifton-Bligh PB, et al. *J North Amer Meno Society*, (2001)<sup>15</sup>

**Objective:** This study was undertaken to evaluate the effects of varying doses of phytoestrogens on lipid and bone metabolism in postmenopausal women.

**Method:** A novel red clover isoflavone preparation containing genistein, daidzein, formononetin, and biochanin was administered to 46 postmenopausal women in a double-blind protocol after a single-blind placebo phase and followed by a single-blind washout phase. Patients were randomized to receive either 28.5 mg, 57 mg, or 85.5 mg of phytoestrogens daily for a 6-month period.

**Results:** At 6 months, the serum high-density lipoprotein cholesterol had risen significantly by 15.7–28.6% with different doses ( $p=0.007$ ,  $p=0.002$ ,  $p=0.027$ ), although the magnitude of the response was independent of the dose used. The serum apolipoprotein B fell significantly by 11.5–17.0% with different doses ( $p=0.005$ ,  $p=0.043$ ,  $p=0.007$ ) and the magnitude of the response was independent of the dose used. The bone mineral density of the proximal radius and ulna rose significantly by 4.1% over 6 months with 57 mg/day ( $p=0.002$ ) and by 3.0% with 85.5 mg/day ( $p=0.023$ ) of isoflavones. The response with 28.5 mg/day of isoflavones was not significant. There was no significant increase in endometrial thickness with any of the doses of isoflavone used.

**Conclusion:** These results show that the administration of an isoflavone combination extracted from red clover was associated with a significant increase in high-density lipoprotein cholesterol, a significant fall in apolipoprotein B, and a significant increase in the predominantly cortical bone of the proximal radius and ulna after 6 months of treatment.

# Safety

## Breast Safety

- A double-blind randomized controlled trial of isoflavones in the treatment of cyclical mastalgia, Ingram DM, et al. *The Breast*, (2001)<sup>15</sup>

**Objective:** Cyclical mastalgia is very common in Western populations and is believed to have a hormonal basis. Isoflavones are a subgroup of phytoestrogens which we hypothesized might be a simple and effective means of therapy as they act as a weak anti-oestrogen in pre-menopausal women and have no side-effects.

**Method:** A double-blind randomized control trial of either placebo, 40 mg or 80 mg of isoflavones was undertaken after an initial 2 month single-blind 'Placebo Lead-in' to exclude women with a significant placebo response. Eighteen women were randomized to the treatment phase of the trial. Nine of the 12 women on treatment had a worthwhile improvement in their pain compared to only two of six on placebo.

**Results:** The reduction in pain was 13% for placebo, 44% for 40 mg of isoflavone per day and 31% for 80 mg per day.

**Conclusion:** There have been no previous clinical studies of isoflavones for the treatment of mastalgia and the benefit demonstrated in this study adds another valuable arm to therapy.

- Red clover-derived isoflavones and mammographic breast density: a double-blind, randomized, placebo-controlled trial, Atkinson C, et al. *Br Cancer Res*, (2004)<sup>17</sup>

**Objective:** Isoflavones are hypothesized to protect against breast cancer, but it is not clear whether they act as oestrogens or anti-oestrogens in breast tissue. Our aim was to determine the effects of taking a red clover-derived isoflavone supplement daily for 1 year on mammographic breast density.

**Method:** A total of 205 women (age range 49–65 years) with Wolfe P2 or DY mammographic breast patterns were randomly assigned to receive either a red clover-derived 40mg isoflavone tablet or placebo. Change in mammographic breast density, serum oestradiol, FSH, LH, menopausal symptoms and lymphocyte tyrosine kinase activity from baseline to 12 months were assessed.

**Results:** A total of 177 women completed the trial. Mammographic breast density decreased in both groups but the difference between the treatment and placebo was not statistically significant. There was a significant interaction between treatment group and oestrogen receptor (ESR1) PvuII polymorphism for the change in estimated percentage breast density (mean  $\pm$  standard deviation): TT isoflavone 1.4  $\pm$  12.3% and TT placebo -9.6  $\pm$  14.2%; CT isoflavone -5.2  $\pm$  12.0% and CT placebo -2.8  $\pm$  10.3%; and CC isoflavone -3.4  $\pm$  9.7% and CC placebo -1.1  $\pm$  9.5%.

**Conclusion:** In contrast to studies showing that conventional hormone replacement

therapies increase mammographic breast density, the isoflavone supplement did not increase mammographic breast density in this population of women. Furthermore, there were no effects on oestradiol, gonadotrophins, lymphocyte tyrosine kinase activity, or menopausal symptoms.

- Red clover isoflavones are safe and well tolerated in women with a family history of breast cancer, Powles TJ, et al. *Meno Inter*, (2008)<sup>18</sup>

**Objective:** To assess the safety and tolerability of a standardized 40 mg red clover isoflavone dietary supplement (Promensil) in women with a family history of breast cancer.

**Method:** Healthy women aged 35–70 years (n = 401) with at least one first-degree relative with breast cancer received red clover isoflavones or placebo for three years in a randomized, double-blind, placebo controlled trial. Participants were assessed clinically and blood samples taken for biochemical analysis every six months. In addition, study participants underwent mammography, bone density and transvaginal ultrasound (postmenopausal women only) once per year.

**Results:** No significant differences in breast density, endometrial thickness, serum cholesterol, follicle stimulating hormone levels and bone mineral density were detected between those taking red clover isoflavones and placebo. In postmenopausal women, some significant differences in bone marker levels were seen between active and placebo groups, at six months and at 12 months. The adverse event profile was similar across all red clover isoflavone and placebo groups.

**Conclusion:** This three-year study supports the growing body of evidence that treatment with red clover isoflavones is safe and well tolerated in healthy women. Supplements containing red clover isoflavones did not adversely affect breast density, skeletal strength or cardiovascular status. In postmenopausal women, endometrial status was not adversely affected. The adverse event profile was similar between red clover isoflavones and placebo and endocrine status did not differ

## Endometrial Safety

- Red clover isoflavones are safe and well tolerated in women with a family history of breast cancer Powles TJ, Meno Inter, (2008)<sup>18</sup>

**Objective:** To assess the safety and tolerability of a standardized 40 mg red clover isoflavone dietary supplement (Promensil) in women.

**Method:** Healthy women aged 35–70 years (n = 401) Study participants underwent mammography, bone density and transvaginal ultrasound (postmenopausal women only) once per year.

**Results:** No significant differences in endometrial thickness, follicle stimulating hormone levels and bone mineral density were detected between those taking red clover isoflavones and placebo. The adverse event profile was similar across all red clover isoflavone and placebo groups.

**Conclusion:** This three-year study supports the growing body of evidence that treatment with red

clover isoflavones is safe and well tolerated in healthy women. In postmenopausal women, endometrial status was not adversely affected.

- Effect of red clover isoflavones (Promensil) versus placebo on uterine endometrium, vaginal maturation index and the uterine artery in healthy postmenopausal women. Woods R, et al. *Brit Meno Annual Conference Manchester, UK* (2003)<sup>19</sup>

**Introduction:** In today's society there are a significant number of health-aware and environment-conscious women who are seeking alternative, more natural sources of hormones. Plant produce substances, with oestrogen-like effects, called phytoestrogens. There is currently much interest in phytoestrogens, because they may not carry the same risks of HRT to the endometrium or breast due to SERM-like activity. However, few products specific studies exist to confirm this. The aim of the study was to evaluate and compare the efficacy and safety of Promensil versus placebo on endometrial thickness, the indices of uterine blood flow to the uterus and the vaginal maturation index (VMI).

**Method:** A prospective, randomised, double blind, placebo controlled, crossover trial with two eight weeks phases was performed in 29 postmenopausal women. Participants received either 80 mg Promensil (red clover isoflavones, Novogen, Australia) daily or placebo for the first treatment phase for eight weeks, followed by a two weeks "wash out" on placebo, then a further eight weeks on the reverse treatment. Doppler ultrasonography was used to measure the endometrial thickness and pulsatility index (PI) of the uterine artery at the

beginning and the end of each study phase. Vaginal smears were also collected to measure the VMI.

**Results:** After eight weeks' treatments, for both study phases combined, there was no increase in the endometrial thickness for Promensil or placebo from base line (2.4 $\pm$ 0.9 vs 2.4 $\pm$ 0.5mm) to week eight (2.5 $\pm$ 0.9 vs 2.3 $\pm$ 1.0 mm). Both groups decreased but there was no difference between Promensil and placebo for the change in PI from base line (-0.08 $\pm$ 1 vs -0.5 $\pm$ 1). The VMI improved significantly for the Promensil group compared to placebo for the change in percentage of cells in the superficial layer for base line (6 $\pm$ 1 vs -4 $\pm$ 14%, P=0.035), and approached significance for the percentage of cells in the parabasal layer. There were no treatment emergent adverse effects.

**Conclusion:** This is a first study to report the effects of Promensil to aid vaginal atrophy without an increase in endometrial thickening. These and the uterine artery findings are consistent with phytoestrogens binding preferentially to the beta oestrogen receptor (expressed in vaginal tissue), rather than the alpha oestrogen receptor (expressed in the uterus and uterine artery). Longer studies assessing the endometrium would be needed to confirm this positive effect.

# Promensil is a natural women's health brand made from Red Clover Isoflavones.



Recognised worldwide by Healthcare Professionals & Consumers, Promensil is clinically tested to safely and effectively help relieve menopause and post menopause symptoms.

# Menopause Treatment Algorithm

## Other Endometrial Studies

- Hale GE, et al. *Menopause, Jour NAMS* (2001)<sup>21</sup>  
 Endometrial biopsies were performed on 30 pre-menopausal women during the late proliferative stage of the menstrual cycle. After 12 weeks dosing with 50 mg red clover isoflavone concentrate, there was no change in proliferative index compared to a placebo group.

- Woods R, et al. *Journal of the British Menopause Society* (2003)<sup>22</sup>  
 A total of 29 women took part in a crossover trial with two eight-week phases. No increase in endometrial thickness measured by Doppler ultrasonography was observed in Promensil or placebo and no difference was observed between groups for uterine blood flow.

- Baber R, et al. *Climacteric* (1999)<sup>23</sup>  
 Vaginal ultrasound was performed in 43 postmenopausal women after 12 weeks dosing at 40 mg per day. There was no change in the endometrial thickness of the uterus from baseline measures.

Promensil is an appropriate first line treatment for mild to moderate vasomotor symptoms. The treatment algorithm (Figure 1) adapted from Nachtigall et al. (2005)<sup>24</sup> recommends that mildly and moderately symptomatic women first trial clinically proven complementary therapies, such as Promensil, for an 8–12 week period. If symptoms are not managed sufficiently then Hormone Therapy (HT) is an appropriate second line treatment option. For severely symptomatic women who are averse or contraindicated to HT, red clover isoflavones (eg Promensil) are an alternative approach that can be considered.

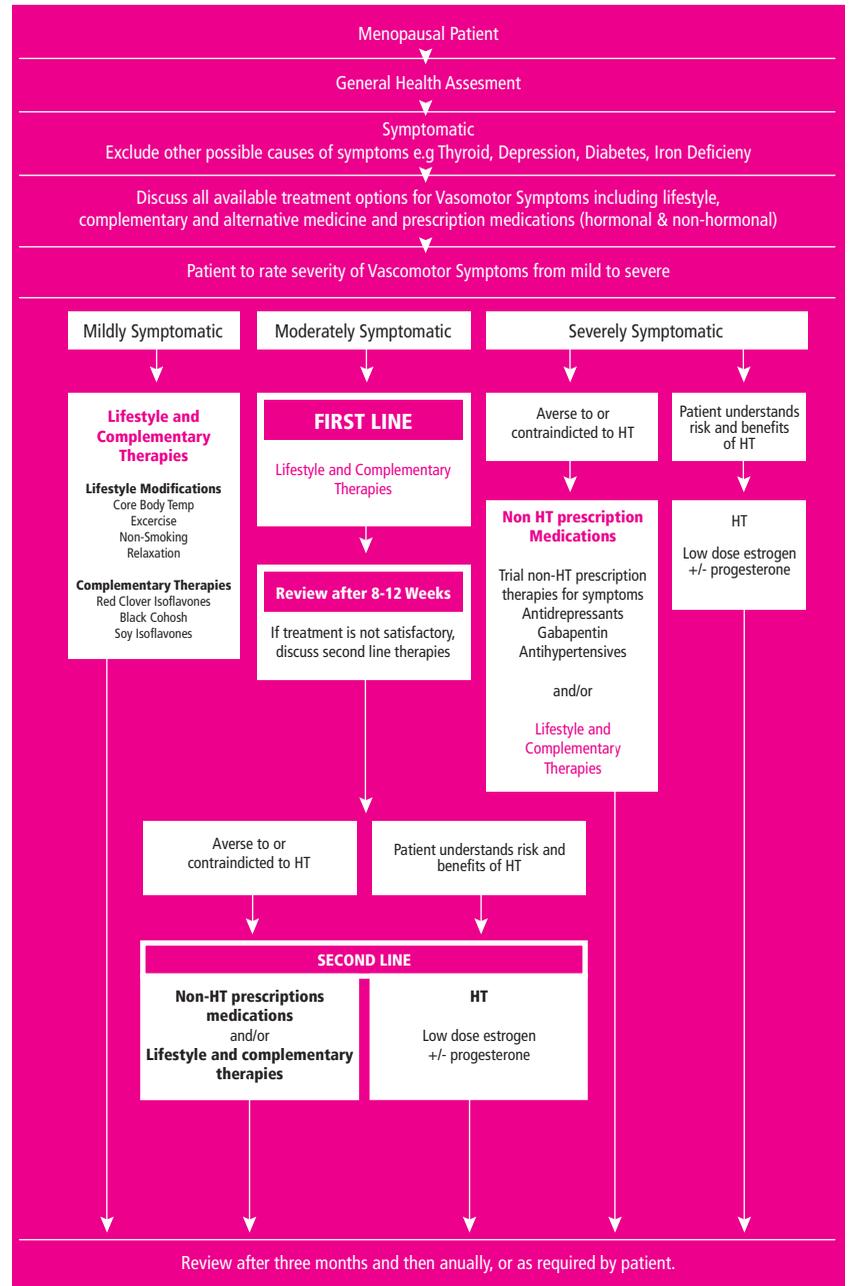
Women who are not appropriate for the conservative use of HT, and therefore those who should be excluded from this algorithm, may include women with premature ovarian failure, high risk of osteoporosis, or women who experience significant menopause symptoms in addition to vasomotor instability such as vaginal dryness, lethargy or pruritus.

Mildly symptomatic women should be counselled about lifestyle measures such as core body temperature regulation, exercise, smoking cessation and relaxation techniques, possibly in combination with a complementary therapy such as Promensil.

For moderately symptomatic women, a 12 week trial of lifestyle modifications in combination with a complementary therapy should be commenced. Patient's expectations about the degree of symptom relief should be managed, as this approach may not ameliorate symptoms completely. If the patient does not experience satisfactory reduction in hot flushes by the end of the trial period, she may be prescribed low dose HT as the second line.

For patients in whom HT is contraindicated or who decline such therapy, a non-hormonal prescription medication could be trialled.

For women who are severely symptomatic, HT is the appropriate first line treatment unless contraindicated or a patient has a personal aversion to HT.



HT: Hormone Therapy

APRIL JOGC AVRIL 2006 • 285

# Promensil Range

## For Menopause



### Promensil Menopause

Each tablet contains: *Trifolium pratense* (red clover) extract equivalent to dry herb 2.5 g standardised to contain 40 mg isoflavones

Purpose: Helps relieve menopause symptoms

Dosage: 1 tablet per day



### Promensil Menopause Double Strength

Each tablet contains: *Trifolium pratense* (red clover) extract equivalent to dry herb 5 g standardised to contain 80 mg isoflavones

Purpose: For women in need of extra support to reduce hot flushes and night sweats

Dosage: 1 tablet per day

## For After Menopause



### Promensil Vitality

Each tablet contains: *Trifolium pratense* (red clover) extract equivalent to dry herb 2.5 g standardised to contain 40 mg isoflavones, 1278 mg Calcium Carbonate (equivalent to Elemental Calcium 500 mg), Cholecalciferol (Vitamin D3) 3.5 mcg

Purpose: Helps prevent osteoporosis and may help maintain heart health after menopause

Dosage: 1 to 2 tablets per day

Always read the label and use only as directed. If symptoms persist see your healthcare professional. Vitamins can only be of assistance if dietary vitamin intake is inadequate.

For more information: [www.promensil.com](http://www.promensil.com)

