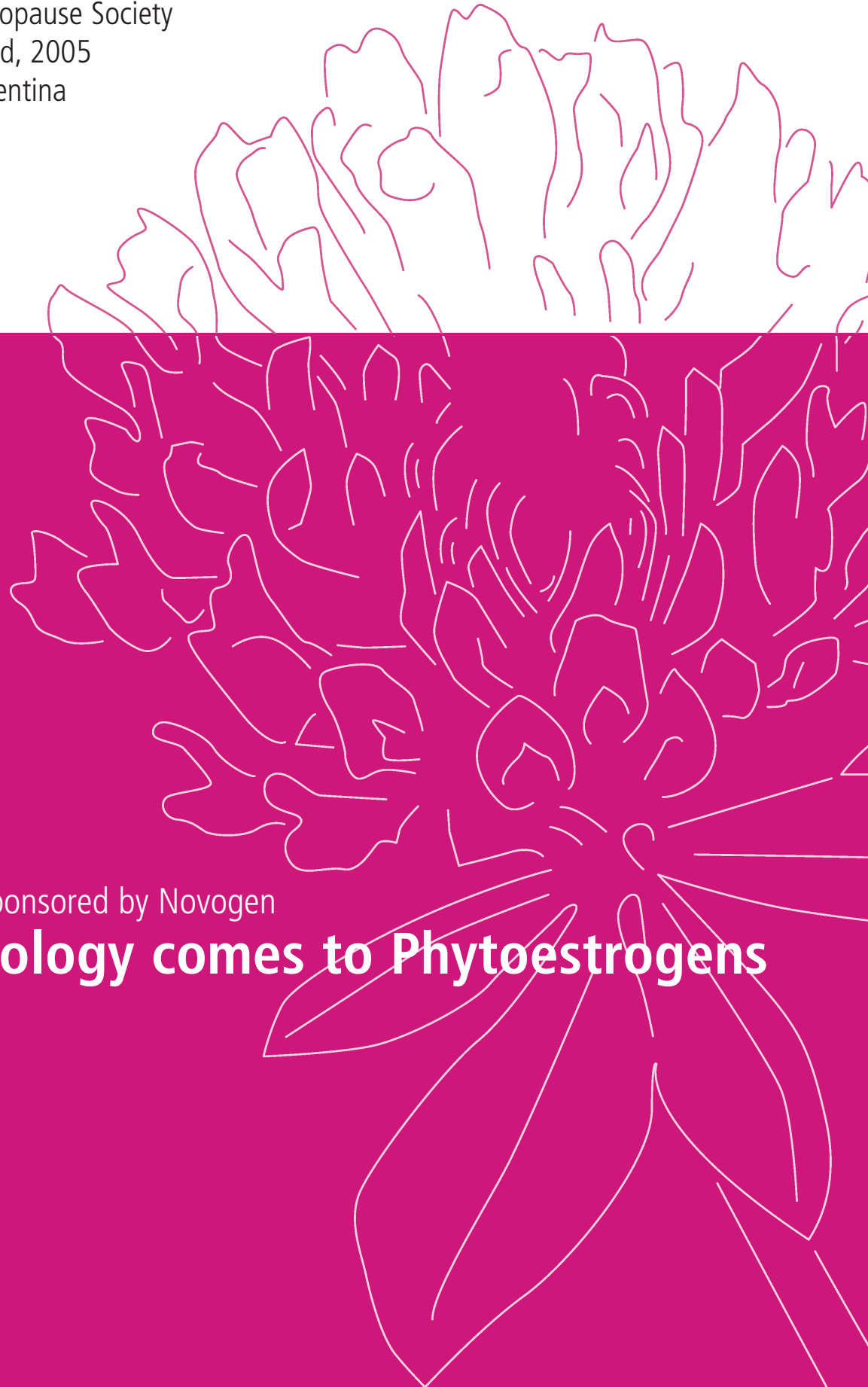


# 11th World Congress on The Menopause

International Menopause Society

October 18th-22nd, 2005

Buenos Aires, Argentina



A symposium sponsored by Novogen

## Pharmacology comes to Phytoestrogens

**promensil**<sup>™</sup>

The patented red clover isoflavone treatment for menopause

## Stephen Barnes

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Professor of Pharmacology & Toxicology at the University of Alabama at Birmingham (UAB). Secondary appointments in the Departments of Biochemistry and Molecular Genetics, Genetics, and Environmental Health Sciences. Dr Barnes is the Director of the UAB Center for Nutrient-Gene Interaction (CNGI) in Cancer Prevention, Associate Director of the Purdue-UAB Botanicals Center for Age-Related Disease. His research interests are on the application of mass spectrometry in biomedical research (small molecules and polypeptides), the prevention of cancer by dietary components with a particular interest in isoflavones and other polyphenols, and biochemistry, chemistry and molecular biology of the amino acid conjugation of bile acids.

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## Understanding isoflavone biology and actions

Phytoestrogens (plant estrogens) are diphenolic compounds used by plants as signaling molecules to attract soil bacteria and as phytoalexins for plant defense. In man, they are potentially useful compounds for the prevention and treatment of several chronic diseases and conditions. Phytoestrogens are synthesized in plants from phenylalanine and malonyl CoA via flavonoids precursors. They are present in large concentrations (1-3mg/g) in soybeans, red clover and in the root of the Kudzu, an overactive vine. Phytoestrogens are typically present in the plant as O-linked glycosidic conjugates. The chemistry of phytoestrogens is strongly influenced by the processing used to prepare foodstuffs and enriched dietary supplements. Reverse-phase HPLC is a useful tool to obtain a chemical fingerprint of the phytoestrogen content of a test food or supplement. The bioavailability of phytoestrogens is highly variable (up to 10-fold) due to different metabolism between subjects. Phytoestrogens are hydrolyzed by gut bacteria, and enzymes in the small intestine. Further metabolism occurs because of anaerobic bacteria, other enzymes in the small intestine and in the liver, as well as non-hepatic peripheral sites. The phytoestrogens and metabolites may be present in physiological subcompartments such as prostatic fluid in very high concentrations, highlighting the importance of measuring the right material for the disease being studied. LC-tandem mass spectrometry is capable of accurately measuring phytoestrogens and metabolites in the low to sub-nanomolar concentrations. Equol, a bacterial metabolite, is found in very different concentrations in animals and humans. In animals (rats, mice, dogs, monkeys, etc.) equol is the major circulating isoflavone metabolite, whereas only one in three human subjects is an equol producer. A different class of phytoestrogens, C-glycosides, is present in dietary supplements based on kudzu roots. These compounds behave quite differently to the O-glycosides in soy and red clover due to their metabolic stability – they are taken up into the blood without hydrolysis. They appear to have impact on glucose metabolism in a model of diabetes. In summary, phytoestrogens have a complex chemistry that undergoes further changes after their consumption and may account for their physiologic properties.

# Lila Nachtigall

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Professor of Obstetrics and Gynecology at the Department of Obstetrics and Gynecology New York University School of Medicine. Dr Nachtigall developed and currently directs the women's Wellness Division of Gynecology at New York University Medical Center. In addition to serving as a trustee for the North American Menopause Society and Secretary of the Board, she is a past President of the North American Menopause Society. Dr Nachtigall is also past President of the Bellevue Obstetrical and Gynecological Society. She was Chair of the Joint Task Force on Women's Issues at New York University School of Medicine and is now a member of the Permanent Committee. Dr Nachtigall is now Chairman of the Board of the Foundation for Women's Wellness. Dr Nachtigall has published and lectured widely on all aspects of hormone replacement therapy.

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## What do we know about the clinical actions of isoflavones?

There is an increasing trend for use of complementary and alternative medicines (CAM) for symptomatic relief among menopausal women. Isoflavones have received considerable interest in the clinic.

Isoflavones have a chemical structure similar to steroidal estrogens, and are capable of binding to estrogen receptors (ER) $\alpha$  and  $\beta$ . Isoflavone binding to ER $\beta$  (found predominantly in bone and blood vessels) is greater than that to ER $\alpha$  (found predominantly in breast and uterus). Isoflavones are found in significant quantities in soy beans, legumes and red clover (*Trifolium pratense*). Red clover has a high content of the isoflavones biochanin A and formononetin, while soy contains predominantly genistein, daidzein and glycitein.

Assessing the efficacy of soy isoflavones is challenging due to the variation in dosages, patient characteristics and outcome measures in clinical trials. In many of the trials composition of the soy isoflavones used is not specified and some preparations may not be standardized.

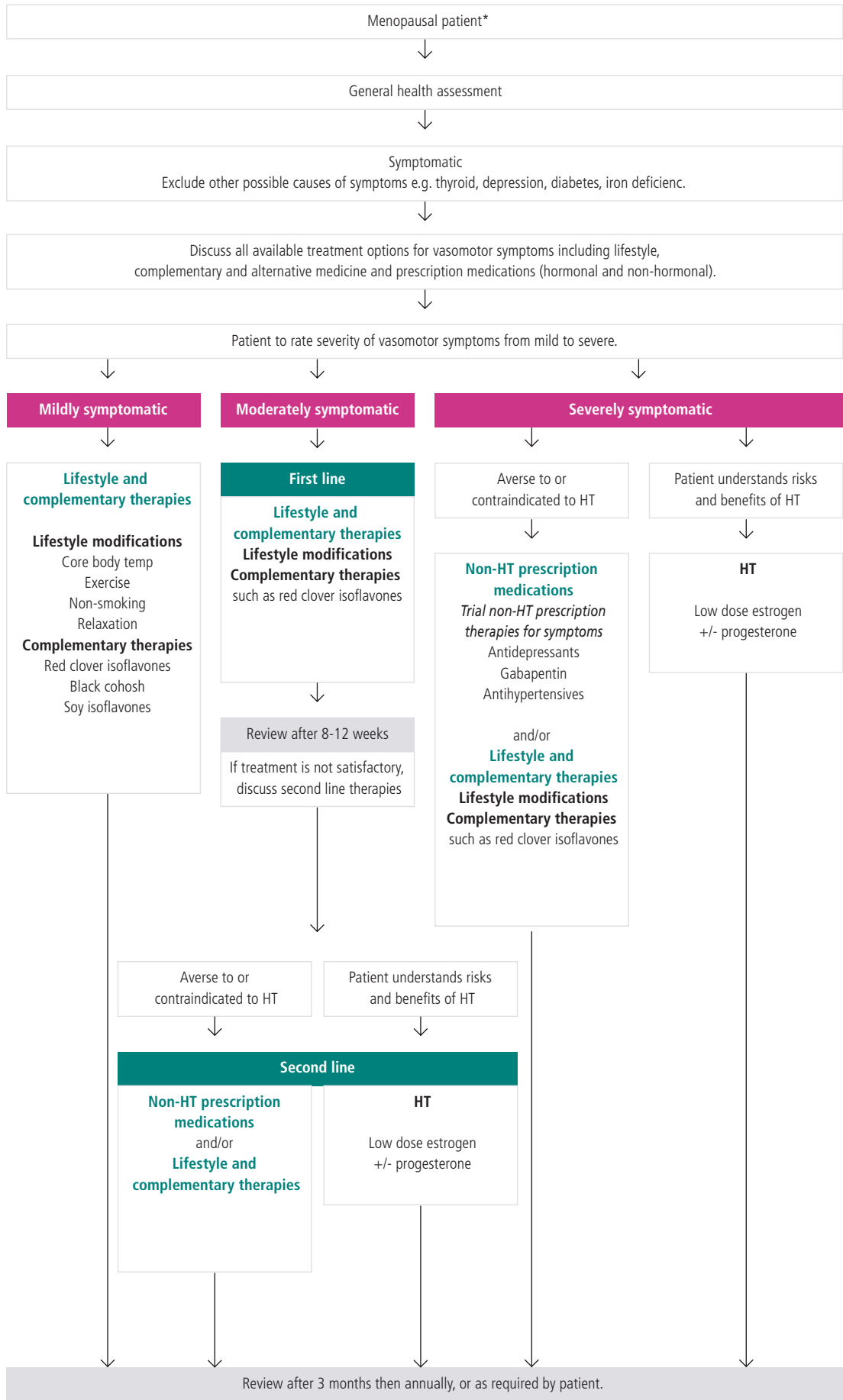
Five placebo-controlled studies evaluating the use of red clover isoflavones in the treatment of vasomotor symptoms have been conducted. Whilst the doses of red clover isoflavones (40-160mg) and the duration of treatment (12-16 weeks) varied in these studies, all showed a numerical reduction in the number of hot flashes compared to placebo. However the differences only reached statistical significance in two out of the five studies.

Red clover isoflavones (40mg) have also been assessed for effects on breast density in a 12-month double-blind randomised placebo controlled trial. Red clover isoflavones (40mg/day) have also been assessed for their proliferative effect on the endometrium via transvaginal ultrasound and found no increased endometrial thickness over 3 months of use.

In addition to vasomotor symptoms and safety parameters, clinical trials have assessed other conditions relevant to the menopause. Studies have assessed short term effects on lipids, arterial compliance, and bone sparing effects.

The evidence to date suggests that isoflavones are a safe alternative potentially offering some moderate benefits for menopausal women. Based on the clinical data for CAM and the growing trend to move away from prescription hormone therapy, a treatment algorithm has been developed based on symptom severity. The guidelines introduces lifestyle approaches and CAMs such as red clover isoflavones as appropriate first line therapies for mildly and moderately symptomatic women.

**Vasomotor symptom treatment algorithm: a conservative, clinical approach.**  
 Adapted from *Nachtigall et al.*  
 Presented at the 61st SOGC, Quebec City, June 16-21, Canada, 2005.  
 \*Guidelines exclude women with premature ovarian failure or with a high risk of osteoporosis.



## Alan J Husband

PhD, DSc, FASM. Group Director of Research  
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Professor Husband is Group Director of Research for Novogen Ltd, and its oncology subsidiary company, Marshall Edwards, Inc (MEI). Professor Husband holds a professorial appointment at the University of Sydney. During his time in academic research he achieved international recognition for contributions in immunology and pathology. In his current position with Novogen and MEI, which he has held since 1996, he is involved in commercialisation of new technologies developed by the group. During his time with the company Professor Husband has managed the drug discovery and clinical trial program culminating in the current entry into Phase III of the lead anti-cancer compound phenoxodiol, now awarded fast track status by the FDA for the treatment of ovarian and prostate cancers.

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## New pharmaceutical developments from isoflavone research

Compounds based on a flavonoid (di-phenolic) ring structure are emerging as a potentially important new class of pharmaceutical compounds with a broad range of biological activities most prominent of which are their potential role as anti-cancer agents. These compounds exert a wide range of up-regulating and down-regulating effects on signal transduction processes within cells in both plants and animals. The observation that populations consuming vegetarian based diets have a lower incidence of many degenerative diseases and some cancers has led to speculation that these compounds, or synthetic analogues, may be of therapeutic value. The evidence supporting this hypothesis is reviewed, and examples of attempts to develop new therapeutics based on dietary isoflavones or novel isoflavonoid structures in maintaining health and in cancer treatment and management are provided. One of these compounds, phenoxodiol, is now in human clinical trials and has shown promise in patients with recurrent ovarian cancer where the cancer is refractory or resistant to standard chemotherapy, and in patients with hormone-refractory prostate cancer.

**Novogen** Limited is the Australian and NASDAQ listed company that is at the forefront of isoflavone research and development. Novogen has a commitment to products based on rigorous science, medical endorsement, and excellence in manufacturing.

Isoflavones have always been part of the human diet, although their presence in human blood was not detected until the early 1980s. Since then, isoflavones and their metabolite compounds have received particular scientific and medical attention. Their potent biological effects on a range of human cells have now been confirmed, as has the link between the extent of dietary isoflavone consumption and the incidences of major diseases.

Novogen developed the science and understanding of how isoflavones could help to reduce menopause and pre-menstrual symptoms in the early 1990's. A result of the company's pioneering research the company has been granted patents in USA, Canada, Europe and Australia. The patents cover tablets or capsules containing any two of the four main isoflavones, biochanin, formononetin, daidzein and genistein.

The isoflavones used in Novogen's products are extracted from red clover using state-of-the-art technology under pharmaceutical conditions, meeting Good Manufacturing Practice standards. Novogen continues an extensive international clinical study program to explore the health benefits of dietary isoflavones in Promensil™ for menopause, and Trinovin™ for men's prostate health.

Novogen's scientific understanding of isoflavones also has led to the isoflavone metabolite programs, which have synthetic compounds in human clinical trials in USA and Australia, developing drug therapies to treat cancer, inflammatory and cardiovascular diseases.

### **Promensil. The first-line choice**

- Complementary menopause treatments are an important option for women with a contraindication or personal aversion to HT.
- Promensil can effectively relieve mild-to-moderate menopause symptoms.
- Supported by clinical efficacy and tolerability data, Promensil is an appropriate first line treatment for mild to moderate menopause symptoms.

### **Worldwide, doctors are turning to Promensil**

- Promensil is now available in 13 countries, with over 220 million daily doses taken worldwide since launch.
- In the UK, Australia and Canada, Promensil is the No. 1 doctor-recommended complementary treatment for menopause.
- Since 2004 Promensil has been issued with patents in USA, Europe, Canada and Australia.

### **Promensil – red clover isoflavones**

- Promensil is an extract of mature red clover plants, containing 40mg aglycone isoflavones.
- Red clover is a rich source of all four major isoflavones.
- The four major isoflavones (biochanin, formononetin, genistein and daidzein) possess significant biological estrogenic activity, and other hormone independent biological activities.

### **Clinical efficacy**

- Over 1,000 women have been enrolled into clinical trials with Promensil.
- Promensil significantly reduces the frequency and severity of hot flushes.
- Promensil has a beneficial effect on bone and cardiovascular health.

### **Tolerability and safety**

- No product-related side effects have been observed with Promensil and the safety profiles are equivalent to that of placebo.
- There was no product-related weight gain.
- Throughout the studies, haematological and biochemical parameters remained unchanged from baseline.
- No breakthrough bleeding was observed in any of the studies after 3 months.
- There was no evidence of endometrial thickening by ultrasound after 3 months.
- There was no increase in breast density after 12 months.

***For further information on the presentations at the 11th World Congress on the Menopause,  
visit [www.promensilclinical.com](http://www.promensilclinical.com) or email [promensil@novogen.com](mailto:promensil@novogen.com)***

**promensil**<sup>™</sup>

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