**COMPLAINTS RESOLUTION PANEL FINAL DETERMINATION**

**Complaint 1-1299 (Promensil)**

## The complaint

1. Professor Alastair MacLennan, Associate Professor of Obstetrics and Gynaecology at the University of Adelaide, complained that advertisements for Promensil misrepresent the published data on its safety and efficacy. The only advertisement over which the Panel has jurisdiction is that published in The Weekend Australian Colour Magazine dated 4-5 December 1999. That advertisement contained:

   (i) the headline "Now you can support your belief in natural therapy with scientific evidence",
   (ii) the sub-heading "Proven studies",
   (iii) the statements: "Promensil's effectiveness has been proven in clinical trials around the world. These studies have demonstrated a significant reduction in menopausal symptoms such as hot flushes, night sweats and mood swings", and
   (iv) the statement "Promensil – a proven natural alternative for menopause".

2. Professor MacLennan, who is editor-in-chief of "Climacteric", the journal of the International Menopause Society, relies in particular on two randomised placebo controlled trials (references 11 and 15 in the advertisement), the results of which were published in the June 1999 issue of that journal and which he says were negative.

3. In response the sponsor, Novogen Limited, relied upon the facts that the advertisement was approved before publication for compliance with the Therapeutic Goods Advertising Code; that the references cited in the advertisement and other, more recent studies, meet the levels of evidence proposed in draft CMEC guidelines to support claims of the kind in question for listed products and on "a number of current peer reviewed publications and trial data presented at international peer review meetings". Novogen stated that the advertisement was intended to respond to criticism of natural therapies by showing there was "no lack of 'science'" behind the claims for the product.

4. Dr MacLennan criticised the studies on which Novogen relied and contended the two randomised placebo-controlled double-blind trials had been ignored.

## The Panel's interim determination

5. In its interim determination dated 31 January 2000, the Panel noted that under the scheme of Division 5 of the Therapeutic Goods Regulations, approval of an advertisement prior to publication is not a defence to a complaint, which the Panel is obliged to determine on the material put before it.

6. The Panel also noted from s.28(6) of the Therapeutic Goods Act and Regulation 42ZF(2)(f) that the levels of evidence proposed by CMEC relate to

the process of obtaining listing and do not necessarily govern advertising of listed products. It found that compliance with the evidentiary requirements for listing may not necessarily suffice to defend a complaint that advertised claims breach the Code. Advertised claims must be assessed by the Panel in the light of the cogency of the evidence and submissions put before it, having regard to the audience to which the advertisement is directed and the meaning to be attributed to the advertisement as a whole.

7. Novogen had not provided to the Panel any of the references cited in the advertisement nor the other references on which it relied. Nor had it addressed the two randomised double-blind placebo-controlled studies and Dr MacLennan's contention that their results were negative.

8. Under these circumstances, in the absence of any further information, the Panel stated that it was minded to find the complaint justified and to request Novogen to withdraw the advertisement from further publication. However, since it was possible that Novogen's confusion over the significance of approval and the place of the draft CMEC levels of evidence in the regulatory scheme might have led it to provide a less than full response to the complaint, the Panel invited Novogen to supply to it within 7 days, a copy of each reference mentioned in the advertisement; any other reference on which it relied and any further submission it may wish to make in response to the complaint.

9. The Panel stated that, should Novogen comply with this request, it was its intention, before making its final determination, to consult CMEC on the question whether the claims": "Promensil's effectiveness has been proven in clinical trials around the world" and "Promensil – a proven natural alternative for menopause" are not justified on the material before the Panel and to give Dr MacLennan and Novogen an opportunity to comment on CMEC's response.

**Subsequent correspondence and procedural issues**

10. Novogen wrote to the Panel on 14 February, 7 March and 15 March 2000. The Panel Secretary wrote to Novogen on 24 February, 1 March and 10 March. That correspondence and all the references enclosed with the Novogen letter of 14 February have been fully considered by the Panel although some parts of the material supplied by Novogen were said to contain confidential matter which Novogen did not wish to be disclosed to Professor MacLennan. The Panel has considered whether Professor MacLennan may have suffered any injustice in being deprived of the opportunity to respond to that material and has formed the view that he has not, because the determination of the Panel would be the same even if none of the material claimed to be confidential had been before it.

11. During the course of that correspondence, it appeared the Panel had not, as contemplated by its procedures (papa 17), sent to the parties for comment material provided by the Advertising Services Manager (ASM) who approved the advertisement. This was done shortly before the Panel met again. Professor MacLennan did not comment on it. Novogen suggested more information be sought by the Panel from the ASM as to why approval was granted. The Panel considered that, since it had before it all the references

upon which the advertised claims were said to be based, while the ASM did not, no useful purpose would be served by acceding to this request.

12. During the course of the correspondence, Novogen questioned the independence of Professor MacLennan in respect to the matter and requested the Panel to ask him "what support he, his partner and his research group have received directly or indirectly from Novogen competitors and specifically from companies marketing hormone replacement therapies over the past 3 years". The Panel regarded this issue as irrelevant to the only material question for determination, namely whether the advertised claims of which complaint was made were supported by the literature. It therefore decided not to accede to Novogen's request.

13. Novogen expressed concern that some of its confidential data including prepublication manuscripts had been passed to the complainant and requested the Panel "to obtain written assurance from the complainant that all data provided to CRP in good faith and for consideration by CMEC will remain confidential". The Panel Secretary informed the Panel that no material claimed to be confidential had been supplied to Professor MacLennan. The Panel accordingly declined the request.

**Panel consideration of the substance of the complaint**

14. Professor MacLennan's specific complaint, as expressed in his fax to the Panel Secretary dated 6 December 1999, was:

> "I do not believe that the data in the references adequately support that Promensil is a proven alternative for menstrual symptoms such as hot flushes, night sweats and mood swings. 'Its effectiveness has' **not** 'been proven in **scientifically valid** clinical trials around the world'".

This is effectively a complaint about the statements in paragraph 1 (iii) above, which have to be considered in the context of the advertisement as a whole, including the other statements set out in paragraph 1.

15. Before the Panel met on 16 March 2000, all members had received copies of all the references provided by Novogen and by the complainant. The Panel decided to consider the material itself before deciding whether or not to seek advice from CMEC.

16. The references cited in the advertisement as supporting the statement set out in paragraph 1 (iii) above are numbered "12-14". The Panel considered each of these.

**Reference**

17. Reference 12 is *"Husband, A. J et al. COST 916 Workshop Phytoestrogen exposure, bioavailability, health benefits and safety concerns. Doorwerth, Holland, April 1998".* The article supplied by Novogen has a different title[1] and the identity of the publication is not apparent from the copy supplied. The Panel has proceeded on the basis that the copy article supplied by Novogen

[1] "The correlation between phenolic estrogen levels and menopause symptoms in women".

is the material referred to in the advertisement on which Novogen relies, especially since the principal author is Novogen's Research Director, who has prepared material forming part of Novogen's submissions to the Panel.

18. The article describes two trials to test the effect on menopausal symptoms of supplementing the diet with isoflavones (placebo v. Promensil, a supplement which contains the four "primary" isoflavones). Pooled data from all subjects of both studies revealed "a significant negative correlation between levels of urinary excretion of all four isoflavones and incidence of flushes", in other words, the higher the level of isoflavones in the urine, the lower the incidence of flushes. However, "about half the subjects in the placebo group recorded high urinary [isoflavone] excretion levels, presumably reflecting dietary intake of isoflavones. This finding was reflected in a high apparent placebo response (35% and 32% mean reduction in hot flushes in placebo group subject[s] in Study 1 and 2 respectively) but in placebo subjects where urinary isoflavones were low a reduction in flushes of only 15% was observed, representing the true placebo effect".

19. The article concluded: "These data confirm that supplementary isoflavones have therapeutic effect, especially if dietary isoflavone intake is low and that the apparent placebo effect in many studies of menopause symptoms may be attributable to dietary sources of isoflavones, a factor which should be controlled for in future menopause symptom trials".

20. The Panel concludes that, because of the high placebo effect, which the authors presume to be attributable to dietary isoflavone intake, it was not demonstrated with statistical significance in these trials that Promensil is more effective than placebo in reducing hot flushes. Accordingly, reference 12 does not support the statements in paragraph 1 (iii) of which complaint has been made.

**Reference 13**

21. Reference 13 is: *"Data on file. Novogen Ltd."* Private information is not published material and therefore cannot answer a complaint that published material does not support an advertisement.

22. In its submission, Novogen relies on a presentation at the 9th International Menopause Society World Congress on the Menopause, Japan, October 17-21 1999 by Dr Arthur Jeri and another, of the Institute of Gynaecology and Reproduction and Montesur Clinic, Climacteric Units, Lima, Peru[2]. It is possible that this was included in the material referenced as 13. This public presentation was made after the advertisement had been submitted for approval in September 1999 but before its publication in the Weekend Australian in December. On the assumption that, in order to avoid the making of misleading and unjustified claims, the relevant date at which supporting evidence must be held is the date of publication of the advertisement, the Panel has considered whether the Jeri presentation supports the claims set out in paragraph 1 (iii) above.

[2] "The effect of isoflavone phytoestrogens in relieving hot flushes in Peruvian postmenopausal women".

23. Reliance on unpublished data is not unusual but the question remains as to whether the body of evidence supports the claims.

24. Professor MacLennan commented that this was a small, non-peer reviewed study that does not provide medium or high level evidence of efficacy or safety.

25. The aim of this "pilot" study was "to test the hypothesis that isoflavone Phytoestrogens (Promensil) in relieving hot flushes in Peruvian post menopausal women and its action by which isoflavone clinical or biological effect is most likely related to an ability to bind to the estrogen receptor because of their structural similarity to estrogens". The test was performed on 30 women and was double-blinded, prospective, placebo-controlled and randomised.

26. The results were a "significant improvement in relieving hot flushes compared with placebo-controlled. After 16 week[s] on treatment a 75% reduction in the incidence of hot flushes was demonstrated ($p<0.001$)".

27. The conclusions were: "The isoflavones are the most potent class of phytoestrogens and the data obtained in this study are **consistent with the hypothesis that** isoflavones favourable influence in relieving hot flushes. In this pilot study we concluded that isoflavone phytoestrogens **may be** an alternative to HRT in reducing vasomotor symptoms. In Peru, there are many reasons why women wish to avoid HRT, yet there are few effective alternatives offered so phytoestrogens would be a natural and current alternative to traditional HRT in selected patients" (emphasis added).

28. The Panel noted that:

    (a) the authors described their own study as a pilot;
    (b) the study was confined to hot flushes and did not address night sweats or mood swings;
    (c) the conclusion that the data are consistent with the hypothesis does not amount to proof that the hypothesis is true; and
    (d) the conclusion that phytoestrogens may be an alternative to HRT does not amount to proof that they are.

    Accordingly, the Panel found the Jeri presentation did not support the claims set out in para 1 (iii) above.

**Reference 14**

29. This reference is to an article by Nachtigall *et al.* Reprinted in *The Female Patient, June 1999*[3]. The article does not report upon studies conduction by the authors but rather reviews many published articles on the subject under discussion. Its examination of Promensil comprises an account of the Baber study on which Professor MacLennan relies and which is examined below. That account appears to be faulty in its contention that the Baber study lacked a control group.

[3] "Nonprescription Alternatives to Hormone Replacement Therapy".

30. Professor MacLennan made the same comment as in para 24 above and stated that Dr Lila Nachtigall presented the study at the November 1999 International Congress "and agreed that much more work is necessary to prove safety and efficacy".

31. The discussion by Nachtigall *et al.* Of menopausal symptoms, under the heading "Phytoestrogens", concludes:

> "Thus, although a few short-term studies on dietary supplementation with phytoestrogens have suggested a beneficial effect of isoflavones on menopausal symptoms, the data are inconclusive".

32. The overall conclusion to the article reads:

> "Many menopausal women are seeking alternatives to HRT. Although most of the popular herbal remedies used by this group have been poorly studied, evidence suggests that phytoestrogens reduce menopausal symptoms and may confer other health benefits. Longer-term and larger studies are needed to assess the effects of isoflavones and other non-prescription herbal agents on all aspects of postmenopausal physiology – especially with regard to climacteric symptoms, the cardiovascular system, bone and mineral metabolism and breast tissue".

33. Having regard to the authors' view that the data are inconclusive and that longer-term and larger studies are needed, the Panel finds the referenced article does not support the claims set out in paragraph 1 (iii) above.

**Conclusion as to the references cited by Novogen**

34. From its consideration of the referenced articles and the Jeri presentation, the Panel is of the view that none of them supports the claims made in the advertisement that Promensil's effectiveness has been proven in clinical trails around the world and that these studies have demonstrated a significant reduction in menopausal symptoms such as hot flushes, night sweats and mood swings.

**The studies relied upon by the complainant**

35. Professor MacLennan relied upon two studies reported in *Climacteric, June 1999*[45] *Knight* was supported by a grant from Novogen. One of the authors of *Knight* was a consultant to Novogen. Two of the authors of *Baber* were employees of Novogen, one of whom being its Managing Director. Both studies are cited in the advertisement (refs 11 and 15) but not in support of the statements set out in paragraph 1 (iii) above. Novogen describes these as "early studies recently published" and says that it is clear that the results were "indicative of Promensil efficacy – whilst not showing statistical significance". Novogen claimed the results of subsequent studies "more clearly demonstrate Promensil's efficacy than the two early studies" but, as

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4 Knight, D. *et al.* "The effect of Promensil, an isoflavone extract, on menopausal symptoms" ("*Knight*").

5 Barber *et al.* "Randomised placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women" ("*Baber*").

mentioned, the studies relied upon by Novogen do not, in the Panel's view, support the claims of which complaint is made.

36. *Knight* reports the results of a randomised, double-blind, placebo-controlled prospective trial of 37 postmenopausal women with symptoms of estrogen deficiency, to assess whether Promensil effects on menopausal symptom scores and biological measures of estrogen activity. The 3 groups studied were placebo, Promensil 40 mg and Promensil 160 mg. There was no significant difference in the incidence of flushes between the three groups at trial conclusion. No differences between the control and the active groups were observed in the subjective scoring of menopausal symptoms. The article concluded:

> "There is a need for further larger studies investigating the areas of clinical effectiveness of isoflavone supplementation in the treatment of menopausal symptoms. Initial indications of biological activity require appropriate assessment of pharmacokinetic properties and dose-response relationships. Although these compounds may well play a complementary role in the treatment of menopausal symptoms and disease associated with estrogen deficiency, issues concerning dose-response relationships, therapeutic variability and side-effects profiles at these doses and effects on long-term diseases associated with estrogen deficiency, remain to be addressed".

37. *Baber* tested the hypothesis that increasing the intake of isoflavones by dietary supplementation may produce a therapeutic effect in reducing the incidence and severity of hot flushes in menopausal women. There was no significant difference between active and placebo groups in the reduction in hot flushes between start and finish time-points. Analysis performed on interim data time-points revealed a substantially greater reduction in flushing in the active group than placebo at 4 and 8 weeks after commencement of treatment, but this was not statistically significant. The combined values for all subjects, regardless of treatment group, revealed a strong negative correlation between the level or urinary isoflavone excretion and the incidence of hot flushes.

38. *The abstract of* Baber *concluded:*

> "These data do not indicate a therapeutic benefit from dietary supplementation with isoflavones in women experiencing menopausal symptoms, but do indicate that the apparent placebo effect in many studies of menopausal symptoms may be attributable to dietary sources of isoflavones.

39. The article stated:

> "….further studies are required to verify the long-term safety of isoflavone supplementation.
>
> This study failed to show a statistically significant difference between 40 mg of isoflavones (one Promensil tablet per day) and placebo treatment with respect to alleviating menopausal symptoms".

"There is a need for further larger studies investigating the clinical effectiveness of isoflavone supplementation on menopausal symptoms".

40. The Panel is of the view that neither of these studies supports and indeed, they both contradict the claims made in the advertisement that Promensil's effectiveness has been proven in clinical trails around the world and that these studies have demonstrated a significant reduction in menopausal symptoms such as hot flushes, night sweats and mood swings.

41. In the Panel's view, references 12-14, on which Novogen relies, are consistent with and in no way detract from *Knight* and *Baber*, both of which were specifically directed to the very subject-matter of the advertising of which the complaint is made.

**Conclusion as to the complaint**

42. The Panel, having examined all the material put forward by Novogen and Professor MacLennan and having formed a clear view on the complaint, does not consider it necessary to seek advice from CMEC.

43. The Panel finds the complaint justified as a breach of sections 52 of the Trade Practices Act (misleading conduct) and section 53(c) representing that goods have performance characteristics they do not have) and thus a breach of the Therapeutic Goods Advertising Code, paragraph 2.1. It is also a breach of Code paragraphs 3.1.1 (incorrect statements and unverifiable claims), 3.1.2 (designed to arouse unwarranted expectations of product effectiveness) and 3.1.3 (misleading with regard to usage). The Panel does not find the complaint justified as regards safety because the Panel finds the advertisement did not make safety claims.

44. Although the complaint was directed only to the statements set out in paragraph 1 (iii), the Panel examined all the references and the propositions in the advertisement which they were said to support. It found many more instances of claims which did not appear to be justified by the cited references. Accordingly, Novogen should not conclude that the Panel's findings in relation to the specific complaint made constitute acceptance that the other claims in the advertisement are justified by the cited references.

**Sanctions**

45. The Panel regards this as a particularly serious breach of the standards expected in advertising of therapeutic goods to consumers. Novogen's claim that its purpose was to show there was "no lack of science" behind the claims for its product does not sit comfortably with the expressed inconclusiveness of the very references upon which it relies and with the adverse conclusions of the two published studies which it sponsored and supported. Novogen informed the Panel of its ongoing research, the results of which are not yet known. One day those results may prove the claims Novogen made to consumers in December 1999 to be true. But the whole thrust of the advertisement was to reassure consumers that science had by December 1999 already proved their belief in alternative therapy to be well founded. Novogen has not satisfied the Panel that at the time of the advertisement

there was scientifically valid proof that its claims for Promensil were true. Advertising of this kind must stop, lest it bring the complementary medicines industry as a whole into dispute.

46. The Panel requests Novogen Limited to withdraw the advertisement from further publication until the claims are proved to be true by scientifically valid trials, the results of which have been published in peer-reviewed publications and within 14 days of being notified of this request, to provide evidence to the Panel of its compliance.

47. Attention is drawn to the provisions of Regulations 9AC(3) and (4) of the Therapeutic Goods Regulations which permit the Panel to make recommendations to the Secretary in the event of non-compliance with this request, including a recommendation that the listing of the product be cancelled.

Dated 22 March 2000

For the Panel

Alan L Limbury
Chairman