

## 3.2 TIBOLONE

### Summary

There is consistent level I and II evidence that tibolone is more effective than placebo or no treatment, and of equal efficacy to HRT in the treatment of vasomotor and urogenital symptoms. There is limited and conflicting level II evidence that tibolone has an effect on sexual function or sleep disturbances. There is limited level II evidence that tibolone improves global quality of life, but no evidence regarding the effectiveness of tibolone according to menopause-specific global symptom scales. There is level I and II evidence which suggests that while tibolone does cause bleeding, particularly in the early stages of treatment, it is associated with a lower incidence of bleeding than either ERT or continuous EPRT.

### 3.2.1 BENEFITS FOR THE RELIEF OF MENOPAUSAL SYMPTOMS

#### Vasomotor symptoms

##### Existing systematic reviews

Two systematic reviews were identified by the literature search, including one considered to be of good methodological quality (Modelska and Cummings, 2002) and one considered to be poor quality (Moore, 1999) which will not be considered further. The characteristics and quality of the two identified reviews are presented in Table 164. For further details see Appendix B (Section 9.3).

In the Modelska and Cummings (2002) review the literature was searched to August 2001. This resulted in five placebo- or no-therapy controlled RCTs (with a total of 275 patients), in addition to two RCTs with HRT as the comparator (with a total of 457 patients). Whilst the primary outcomes of these studies were vasomotor symptoms (hot flushes/night sweats), the effect of HRT upon other symptoms of menopause and quality of life during menopause were also investigated.

TABLE 164 TIBOLONE: VASOMOTOR SYMPTOMS — EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
Modelska & Cummings (2002)	Systematic review of RCTs (7) <i>Good</i>	Postmenopausal women	Tibolone Oral 2.5 mg	Placebo or HRT	Hot flushes, night sweats, palpitations, backache
Moore (1999)	Systematic review of RCTs (10) <i>Poor</i>	Postmenopausal women	Tibolone Oral 2.5 mg	Placebo or no therapy or HRT	Hot flushes, sweating

See Section 9.3.

Abbreviations: RCT, randomised controlled trial.

The studies included in the Modelska and Cummings (2002) review indicated a significant reduction in hot flushes and sweating in women taking tibolone compared with placebo. When tibolone was compared with ERT and EPRT similar improvements in hot flushes and sweating were seen. However, the results of the tibolone versus ERT comparison should be viewed with caution given the very small sample size (n=20), the absence of a washout period for the cross-over study and the fact that dropouts were not reported. The results presented in the review are summarised in Table 165.

TABLE 165 TIBOLONE: VASOMOTOR SYMPTOMS — RESULTS OF EXISTING SYSTEMATIC REVIEW\* (MODELSKA AND CUMMINGS, 2002)

Study	Design	N (age)	Duration	Outcome and size of effect
<i>Placebo- or no treatment-controlled</i>				
Kicovic 1982	Random, double-blind, cross-over	82	16 weeks/period	39% decrease in hot flushes (0-3 point scale score)
Cittadini 1982	Random, double-blind	60	6 weeks	No significant difference in perspiration, palpitations, irritability or backache.
Nevinny-Stickel 1983	Random, double-blind, cross-over	35 (48-69)	16 weeks/period	Reduction in frequency (p<0.003) and severity (p<0.01) of hot flushes, sweating (p<0.01) and headaches (p<0.02). (0-3 point scale score)
Bedenk-Jaszman 1987	Random, double-blind	60 (44-61)	48 weeks	Reduction in hot flushes (p<0.001), sweating (p<0.01) and fatigue (p<0.05). (0-3 point scale score)
Laan 2001	Random, double-blind	38 (>65)	12 weeks	Reduction in hot flushes (p<0.0005). No change in severity of night sweats.
<i>HRT-controlled — oestradiol valerate</i>				
Crona 1988	Random, double-blind, cross-over	20 (27-37)	18 weeks	Note: all patients had undergone oophorectomy Both treatments improved climacteric symptoms (0-3 point scale score)
<i>HRT-controlled — oestradiol + norethisterone acetate</i>				
Hammar 1998	Random, double-blind	437 (> 53)	48 weeks	Both treatments reduced hot flushes and sweating (0-5 point scale score)

\*Modified from Modelska and Cummings (2002)

## Original studies

Since the literature search conducted for the Modelska and Cummings (2002) review, only two RCTs comparing tibolone to placebo have been published. These RCTs, by Landgren *et al.* (2002) and Meeuwssen *et al.* (2002) were both conducted in northern Europe and are considered to be of good and fair methodological quality respectively. In addition, one study has compared tibolone with EPRT (conjugated equine oestrogen and medroxyprogesterone acetate) and is considered to be of fair methodological quality (Baracat *et al.*, 2002). The main characteristics and quality of the RCTs are summarised in Table 166. For further details see Appendix B (Section 9.3).

TABLE 166 TIBOLONE: VASOMOTOR SYMPTOMS — ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Level II evidence					
Baracat <i>et al.</i> (2002)	RCT, open-label <i>Fair</i>	Postmenopausal women Natural menopause 45-65 years N=85	Tibolone Oral 2.5 mg N=40	CEE (0.625 mg/day) plus MPA (5mg/day) N=45	Hot flushes
Landgren <i>et al.</i> (2002)	RCT, double-blind <i>Good</i>	Postmenopausal women Intact uterus Experiencing vasomotor symptoms 40-60 years N=775	Tibolone Oral 0.625, 1.25, 2.5 and 5.0 mg N=632	Placebo N=143	Hot flushes, night sweating
Meeuwssen <i>et al.</i> (2002)	RCT, double-blind <i>Fair</i>	Postmenopausal women Natural menopause Mean age 54.2 N=85 <sup>a</sup>	Oral Tibolone 2.5 mg N=39	Placebo N=42	Hot flushes, sweating

See Section 9.3.

Abbreviations: CEE, conjugated equine oestrogens; MPA, medroxyprogesterone acetate; RCT, randomised controlled trial.

<sup>a</sup> Only 81 women were included in the analysis.

The results of the two placebo-controlled RCTs and one HRT-controlled RCT are summarised in Table 167. Results relating to the 2.5 mg dose of tibolone are shown only as this is the dose approved for use in Australia. These studies show that the occurrence and frequency of hot flushes and sweats were significantly reduced in women taking 2.5 mg of tibolone compared with placebo. In the head-to-head study, both tibolone and combined HRT were shown to significantly reduce hot flush scores (taking into account frequency and severity) at 12 months compared with baseline. There was no significant difference between the two treatments.

TABLE 167 TIBOLONE: VASOMOTOR SYMPTOMS — RCT RESULTS

Author	Tibolone 2.5 mg/day	Comparator	P value
<b>Placebo-controlled</b>			
<i>Landgren et al.(2002)</i>			
Hot flushes — mean (SD)/24 hrs			
Baseline	8.2 (5.6)	8.1 (4.8)	>0.05
12 weeks <sup>a</sup>	1.9	5.2	< 0.0125
Sweats — mean (SD)/24 hrs			
Baseline	7.5 (6.2)	7.5 (4.9)	>0.05
12 weeks <sup>a</sup>	1.6	4.3	< 0.0125
Percentage of responders <sup>b</sup> — n (%)			
Hot flushes	130 (87.7)	111 (55.0)	< 0.001
Sweats	124 (83.9)	110 (57.3)	< 0.001
<i>Meeuwssen et al.(2002)</i>			
Hot flushes — %			
Baseline	83.3	86.1	0.771
12 months	33.3	65.9	0.007
Nightly sweats — %			
Baseline	81.0	86.1	0.571
12 months	23.1	48.8	0.021
<b>HRT-controlled — CEE/MPA</b>			
<i>Baracat et al.(2002)</i>			
Hot flushes — total score <sup>c</sup>			
Baseline	11.3	12	ns
12 months	0	0	ns

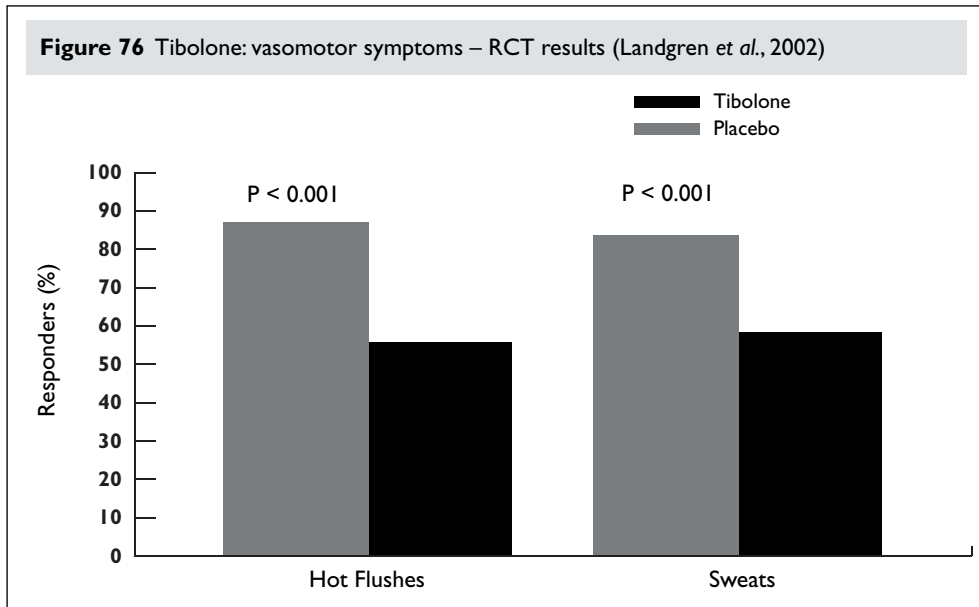
Abbreviations: CEE, conjugated equine oestrogen; MPA, medroxyprogesterone acetate; ns, not significant; SD, standard deviation.

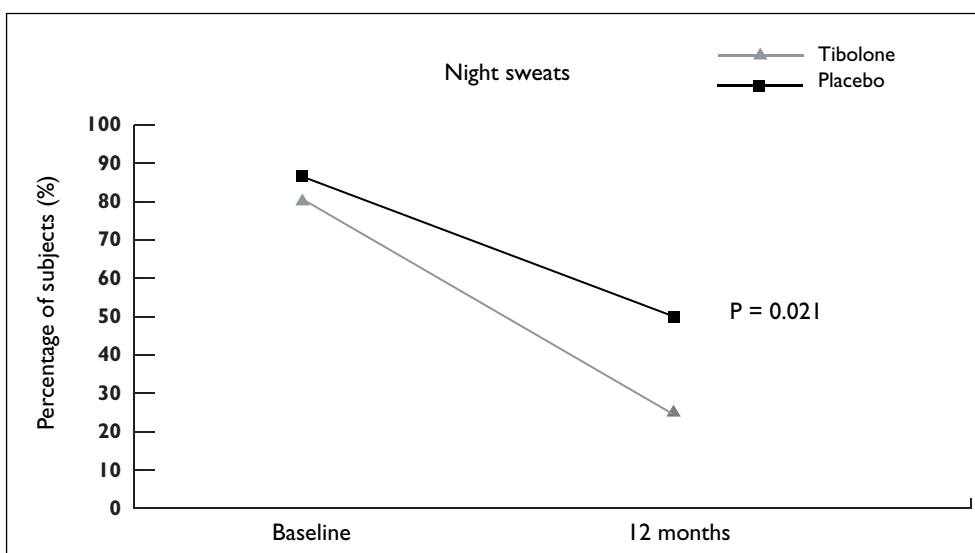
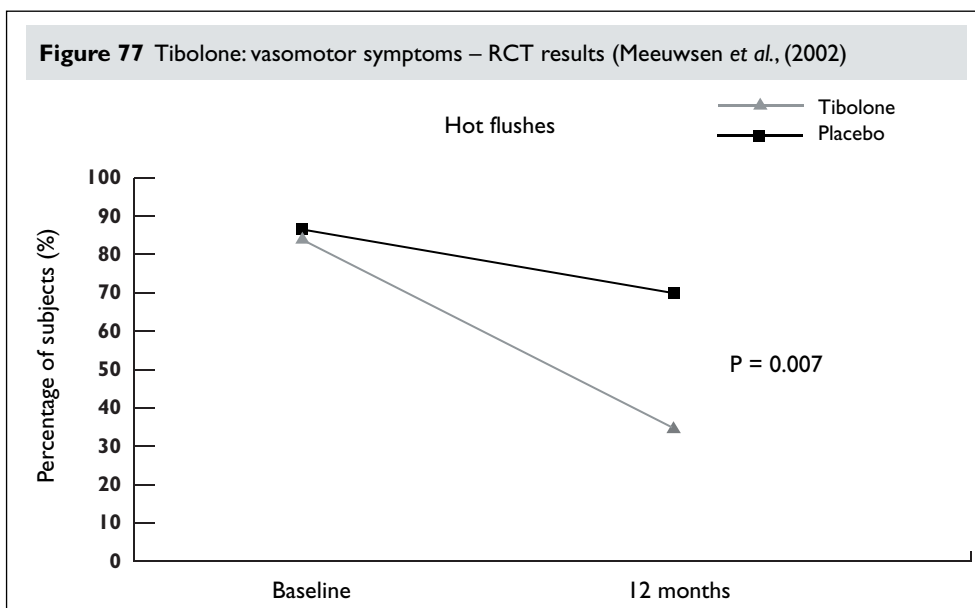
<sup>a</sup> Mean estimated from graph

<sup>b</sup> Includes only patients with  $\geq 3$  episodes per day

<sup>c</sup> Calculated as sum of mean number of hot flushes/day multiplied by respective severity score (1=mild, 2=moderate, 3=severe). Estimated from graph.

Figure 76 and Figure 77 show the results over time in the Landgren and Meeuwssen studies, indicating the presence of a large placebo effect. This reiterates the need for placebo-controlled trials in the assessment of therapies for the vasomotor symptoms of menopause.





Therefore, the results of the three RCTs, coupled with the results of the systematic review of earlier studies by Modelska and Cummings (2002) confirm that 2.5 mg tibolone is effective at reducing the vasomotor symptoms of menopause. The results of the Baracat *et al.* (2002) study suggest that tibolone is as effective as continuous combined EPRT (CEE/MPA) at reducing hot flushes.

## Urogenital symptoms/sexual dysfunction

### Existing systematic reviews

Two systematic reviews provided information regarding the effect of tibolone on urogenital symptoms and/or sexual dysfunction associated with menopause. The review by Modelska and Cummings (2002) assessed sexual dysfunction and was considered to be a good quality review. The review by Moore (1999) assessed both urogenital symptoms and sexual dysfunction and was considered to be a poor quality review. The Moore review will not be considered in relation to sexual dysfunction, however, as this is the only review examining urogenital symptoms it will be considered for this outcome. A summary of the main characteristics and quality of the included systematic reviews is shown in Table 168. For further details see Appendix B (Section 9.3).

TABLE 168 TIBOLONE: UROGENITAL SYMPTOMS/SEXUAL DYSFUNCTION — EXISTING SYSTEMATIC REVIEWS

Study	Study type Study quality	Population No. of studies	Intervention	Comparator	Outcomes
Level I evidence					
Modelska & Cummings (2002)	Systematic review of RCTs (2) <b>Good</b>	Postmenopausal women	Tibolone Oral 2.5 mg	Placebo or HRT	Sexual function
Moore (1999)	Systematic review of RCTs (11) <b>Poor</b>	Postmenopausal women	Tibolone Oral 2.5 mg	Placebo or no therapy or HRT	Sexual function, vaginal symptoms

See Section 9.3.

Abbreviations: RCT, randomised controlled trial.

With regards to vaginal symptoms, the Moore (1999) review reports that in the only placebo-controlled RCT examining the association between tibolone and vaginal symptoms (De Aloysio *et al.*, 1987), the main statistically significant outcome was a 15% reduction in the number of women with vaginal dystrophy in women given tibolone compared with placebo. In the HRT-controlled studies, vaginal symptoms were improved in both treatment groups. The results of the systematic review by Moore (1999) are summarised in Table 169.

TABLE 169 TIBOLONE: VAGINAL SYMPTOMS — RESULTS OF EXISTING SYSTEMATIC REVIEW\* (MOORE, 1999)

Study	Design	N (age)	Duration	Outcome and size of effect
<i>Placebo-controlled</i>				
De Aloysio 1987	RCT Open-label	168	16 weeks	15% reduction in number of women with vaginal dystrophy in women on tibolone (statistically significant)
<i>HRT-controlled — conjugated oestrogens</i>				
Siseles 1995	RCT Open-label	30 (48-62)	24 weeks	Both tibolone and conjugated oestrogens produced maturation of the vaginal epithelium
Egarter 1996	RCT Open-label	129 (53)	26 weeks	Vaginal dryness reduced to low levels by both tibolone and conjugated oestrogens
<i>HRT-controlled — oestradiol + norethisterone</i>				
Larsson-Cohn 1996	RCT Double-blind	315 (>53)	48 weeks	Vaginal dryness scores reduced from slight to almost none by 12 weeks in both tibolone and combined HRT
<i>HRT-controlled — intravaginal oestrogens</i>				
Botsis 1997	RCT Open-label	72	24 weeks	Includes women with atrophic vaginitis Vaginal dryness, pain on intercourse and signs of atrophic vaginitis all improved on both tibolone and intravaginal oestrogens.

Abbreviations: RCT, randomised controlled trial.

\*Modified from Moore (1999)

With regards to sexual function, the results of the Modelska and Cummings (2002) review are summarised in Table 170. The results of the two placebo-controlled trials are inconsistent. The results of the recent Laan study (2001) suggest that tibolone may have an effect on sexual function (compared with placebo), whilst the results of the Neviny-Stickel study (1983) show no significant benefit.

When compared with active HRT treatment (EPRT; oestradiol + norethisterone acetate) tibolone significantly improved three domains (frequency, satisfaction and enjoyment). However, this study was subject to a drop-out rate of almost 30% and the reasons for dropout were not reported.

TABLE 170 TIBOLONE: SEXUAL FUNCTION — RESULTS OF EXISTING SYSTEMATIC REVIEW\* (MODELSKA AND CUMMINGS, 2002)

Study	Design	N (age)	Duration	Outcome and size of effect
<i>Placebo-controlled</i>				
Nevinny-Stickel 1983	Random, double-blind, cross-over	35 (48-69)	16 weeks/period	No sign of differences in libido and mood
Laan 2001	Random, double-blind	38 (>65)	12 weeks	<b>Significant increases in:</b> Arousability (P < 0.001) Sexual fantasies (P < 0.03) Vaginal lubrication (P < 0.001) <b>No change in:</b> Sexual desire (P = 0.08) Frequency of sexual activity
<i>HRT-controlled — oestradiol + norethisterone acetate</i>				
Nathorst 1997	Random, double-blind	437 (>53)	48 weeks	Significant improvement in frequency, satisfaction and enjoyment vs HRT (Swedish version of McCoy's Sex Scale Questionnaire)

\*Modified from Modelska and Cummings (2002)

### Original studies

Two RCTs examining the effect of tibolone on urogenital symptoms have been published since the Moore (1999) review. Both studies present head-to-head comparisons of tibolone against EPRT. One study, by Huber *et al.* (2002) has been deemed to be of poor methodological quality with regards to urogenital symptoms due to the restricted number of subjects included in the analysis of this outcome. The other study by Baracat *et al.* (2002) is of fair methodological quality. The characteristics and quality of these studies are summarised in Table 171. For further details see Appendix B (Section 9.3).

TABLE 171 TIBOLONE: UROGENITAL SYMPTOMS/SEXUAL DYSFUNCTION — ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
<b>Level I evidence</b>					
Baracat <i>et al.</i> (2002)	RCT, open-label <i>Fair</i>	Postmenopausal women Natural menopause 45-65 years N=85	Tibolone Oral 2.5 mg N=40	EPRT CEE 0.625 mg/day plus MPA 5mg/day N=45	Urogenital (vaginal dryness and painful intercourse) and sexual (decreased interest and frequency of episodes)
Huber <i>et al.</i> (2002)	RCT <i>Poor</i>	Postmenopausal women ~ 55 years N=426	Tibolone Oral 2.5 mg N=208	EPRT CEE 0.625 mg/day plus MPA 5 mg/day N=216	Urogenital

See Section 9.3.

Abbreviations: CEE, conjugated equine oestrogen; EPRT, oestrogen + progestogen; MPA, medroxyprogesterone acetate; RCT, randomised controlled trial.

The results of the study by Baracat *et al.* (2002) are summarised in Table 172. There were no significant differences in the improvements between tibolone and HRT in urogenital or sexual symptoms. With regards to painful intercourse, although no difference is reported between tibolone and EPRT (CEE/MPA) at 12 months, the authors state in their report that there was a significant decrease from baseline for all cycles of HRT but only for cycle 5 in the tibolone group. Furthermore, there was a significant difference between groups at cycle 4, with a lesser benefit experienced by the tibolone group.

As the study by Huber *et al.* (2002) is considered to be of poor quality it will not be considered in any detail. However, it should be noted that the results concur with those of the Moore review which show that both tibolone and HRT are effective in reducing the urogenital symptoms associated with menopause.

TABLE 172 TIBOLONE: UROGENITAL SYMPTOMS/SEXUAL DYSFUNCTION — ORIGINAL STUDY RESULTS (BARACAT *ET AL.*, 2002) <sup>A</sup>

	Tibolone 2.5 mg/day	CEE/MPA
<i>Vaginal dryness (%)</i>		
Baseline	50	35
12 months	7	8
<i>Painful intercourse (%)</i>		
Baseline	15	13
12 months	5	0
<i>Decreased sexual interest (%)</i>		
Baseline	52	38
12 months	20	18
<i>Sexual intercourse episodes (mean number/month)</i>		
Baseline	2.2	2.8
12 months	2.5	2.8

Abbreviations: CEE, conjugated equine oestrogens; MPA, medroxyprogesterone; ns, not significant.

<sup>a</sup> Data estimated from graph.

In summary, while the current evidence suggests that tibolone is as effective as HRT in the treatment of vaginal symptoms and sexual dysfunction associated with menopause, it is important to recognise the limitations of this evidence with respect to both quality and quantity.

## Sleep disturbances

### Existing systematic reviews

Two systematic reviews presented data regarding the effect of tibolone on the sleep disturbances associated with menopause (Modelska and Cummings, 2002; Moore, 2002). The characteristics and quality of these reviews are summarised in Table 173. For further details see Appendix B (Section 9.3). While the Modelska review is considered to be of good methodological quality, the review by Moore is considered to be of poor quality and as such would generally be excluded from this review. However, due to the very limited amount of data available regarding sleep disturbances in the Modelska review, data from the Moore review will be included.

TABLE 173 TIBOLONE: SLEEP DISTURBANCES — EXISTING SYSTEMATIC REVIEWS

Study	Study type Study quality	Population No. of studies	Intervention	Comparator	Outcomes
Level I evidence					
Modelska & Cummings (2002)	Systematic review of RCTs (2) <b>Good</b>	Postmenopausal women	Tibolone Oral 2.5 mg	Placebo or HRT	Insomnia
Moore (1999)	Systematic review of RCTs (5) <b>Poor</b>	Postmenopausal women	Tibolone Oral 2.5 mg	Placebo or no therapy or HRT	Insomnia

See Section 9.3.

The data regarding insomnia presented in the two existing systematic reviews are summarised in Table 174. The results are conflicting with some studies showing a benefit of tibolone compared with placebo and others showing no benefit.

TABLE 174 TIBOLONE: SLEEP DISTURBANCES — RESULTS OF EXISTING SYSTEMATIC REVIEWS\*

Study	Design	N (age)	Duration	Outcome and size of effect
Placebo- or no treatment-controlled				
<i>Modelska and Cummings (2002)</i>				
Kicovic 1982	Random, double-blind, cross-over	82	16 weeks/period	28% reduction in insomnia ( $p < 0.001$ ) (0-3 point scale score)
Genazzini 1987	Random, double-blind	30 (36-59)	24 weeks	Relief from hot flushes from the second month of treatment associated with improvement in insomnia.
<i>Moore (1999)</i>				
Kicovic 1981	Random, double-blind, cross-over	82	16 weeks/period	Insomnia statistically improved compared with placebo
Nevinny-Stickel 1983	Random, double-blind, cross-over	35 (48-69)	6 weeks/period	Insomnia showed no statistical difference compared with placebo
Benedek-Jazsmann 1987	Random, double-blind, parallel group	60 (44-61)	52 weeks	Insomnia showed no statistical difference compared with placebo
De Aloysio 1987	Random, open, parallel	168	16 weeks	Insomnia showed no statistical difference compared with placebo
HRT-controlled –conjugated oestrogens				
<i>Moore (1999)</i>				
Egarter 1996	Random, open, parallel group	129 (53)	26 weeks	Insomnia statistically improved in tibolone arm compared with baseline. (unclear if this is the case for HRT also)

\*Modified from Modelska and Cummings (2002) and Moore (1999)

### Original studies

No studies examining the effect of tibolone on sleep disturbance have been published since the literature searches for two systematic reviews were conducted.

## Global menopause symptom, psychological and quality of life scales

### Existing systematic reviews

No systematic reviews were identified which examined the association between tibolone and menopausal symptoms as measured by global scales, psychological wellbeing and quality of life.

### Original studies

Two studies were identified which measured the benefits of tibolone using global menopause symptom or quality of life scales. The study by Meeuwssen *et al.*, (2002) examined the effectiveness of tibolone versus placebo on quality of life, using the Nottingham Health Profile (NHP). This study was considered to be of fair methodological quality. The study by Huber *et al.*(2002) measured the effectiveness of tibolone compared with combined HRT on menopausal symptoms (Greene Climacteric Scale; GCS) and well-being (Psychological General Well-being Index; PGWB). This study was considered to be of poor methodological quality due to the small and variable number of subjects included in the analyses of these outcomes. The main characteristics and quality of these two RCTs are summarised in Table 175. For further details see Appendix B (Section 9.3).

TABLE 175 TIBOLONE: GLOBAL MENOPAUSE SYMPTOM, PSYCHOLOGICAL AND QUALITY OF LIFE SCALES — ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level I evidence					
Meeuwssen <i>et al.</i> (2002)	RCT, double-blind <b>Fair</b>	Postmenopausal women Natural menopause Mean age 54.2 N=85 <sup>a</sup>	Tibolone Oral 2.5 mg N=39	Placebo N=42	NHP
Huber <i>et al.</i> (2002)	RCT <b>Poor</b>	Postmenopausal women ~ 55 years N=426	Tibolone Oral 2.5 mg N=208	EPRT CEE 0.625 mg/day plus MPA 5 mg/day N=216	Greene climacteric scale PGWB

See Section 9.3.

Abbreviations: CEE, conjugated equine oestrogen; EPRT, oestrogen + progestogen therapy; NHP, Nottingham Health Profile; MPA, medroxyprogesterone acetate; PGWB, Psychological General Wellbeing index; RCT, randomised controlled trial.

As there is fair quality evidence available in the Meeuwssen *et al.* (2002) regarding quality of life, only the results of that study will be shown for this outcome. On the other hand, only poor quality evidence is available for menopause-specific quality of life and psychological well-being from the Huber *et al.* (2002). This was a poor quality study because only a selected group of the subjects (ie, those who were compliant with treatment) were included in the analysis.

The results of the quality of life assessment in the Meeuwssen *et al.* (2002) study are shown in Table 176. The only differences between the treatments are seen for sleep (in favour of tibolone) and physical mobility (in favour of placebo). It is unclear whether the study was sufficiently powered to detect a difference between tibolone and placebo.

TABLE 176 TIBOLONE: QUALITY OF LIFE — RCT RESULTS (MEEUWSEN *ET AL.*, 2002)#

Nottingham Health Profile parameter	Assessment	Tibolone N=39 (Mean +/- SD)	Placebo N=42 (Mean +/- SD)	Tibolone vs placebo P value
Emotional reactions	Baseline	6.8 (12.6)	4.9 (10.5)	
	Last visit	2.9 (10.8)	4.9 (10.5)	ns
Energy	Baseline	8.5 (26.2)	7.1 (20.2)	
	Last visit	4.3 (17.4)	10.3 (21.4)	ns
Pain	Baseline	8.0 (18.5)	12.8 (23.2)	
	Last visit	7.1 (19.8)	13.1 (28.4)	ns
Physical mobility	Baseline	4.5 (9.7)	6.9 (10.8)	
	Last visit	3.8 (9.9)	3.0 (9.1)	0.026*
Sleep	Baseline	19.0 (27.1)	15.7 (23.2)	
	Last visit	7.2 (15.6)	15.2 (26.4)	0.046**
Social isolation	Baseline	0.0 (0.0)	1.4 (5.2)	
	Last visit	0.0 (0.0)	1.9 (7.4)	ns
Overall	Baseline	46.8 (70.9)	48.9 (62.4)	
	Last visit	25.3 (45.7)	47.7 (73.1)	ns

\* Table modified from Meeuwssen *et al.*(2002).

Abbreviations: ns, not significant; SD, standard deviation.

Note: The range of scores is 0-100 for the individual domains and 0-700 for the overall score.

\* In favour of placebo

\*\* In favour of tibolone

The Huber *et al.*, (2002) study assessed the effectiveness of tibolone and continuous combined HRT on menopause symptoms globally using the Greene Climacteric Scale (GCS) and on psychological well-being using the PGWB. As this was considered to be a poor quality study the detailed results will not be presented. However, the study found no significant difference between tibolone and continuous combined HRT for both of these outcomes.

### 3.2.2 UNWANTED SIDE EFFECTS

#### Bleeding

##### Existing systematic reviews

The literature search identified two systematic reviews which examined the effect of tibolone on bleeding. These main characteristics of these reviews, by Modelska and Cummings (2002) and Moore (1999) are summarised in Table 177. For further details see Appendix B (Section 9.3).

TABLE 177 TIBOLONE: BLEEDING — EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
Modelska & Cummings (2002)	Systematic review of RCTs (3) <i>Good</i>	Postmenopausal women	Tibolone Oral 2.5 mg	Placebo or HRT	Vaginal bleeding
Moore (1999)	Systematic review of RCTs (5) <i>Fair</i>	Postmenopausal women	Tibolone Oral 2.5 mg	Placebo or no therapy or HRT	Vaginal bleeding

See Section 9.3.

Abbreviations: RCT, randomised controlled trial.

The results of the studies included in the two systematic reviews are summarised in Table 178. These results suggest that while bleeding does occur with tibolone therapy (as shown by the one study comparing tibolone to placebo), bleeding is less frequently caused by tibolone compared with both ERT and continuous EPRT. Modelska and Cummings (2002) concluded that tibolone caused about half as much bleeding as EPRT. Moore (1999) states that when bleeding does occur with tibolone it tends to be during the first three months of therapy.

TABLE 178 TIBOLONE: BLEEDING — RESULTS OF EXISTING SYSTEMATIC REVIEWS\*

Study	Design	N (age)	Duration	Outcome and size of effect
<b>Placebo- or no treatment-controlled</b>				
<i>Modelska and Cummings (2002)</i>				
Berning 2000	Random, double-blind,	94 (>50)	96 weeks	Bleeding occurred in 51% of subjects on tibolone and 22% on placebo ( $P < 0.05$ ).
<b>HRT-controlled — conjugated oestrogens</b>				
<i>Moore (1999) a</i>				
Siseles 1995	Random, open-label, parallel group	30 (48-62)	24 weeks	No bleeding with tibolone
Egarter 1996	Random, open, parallel group	129 (53)	26 weeks	After 1 month significantly less bleeding. After 6 months rates were 4% for tibolone and 27% for oestrogen.
<b>HRT-controlled — intravaginal oestrogens</b>				
<i>Moore (1999) a</i>				
Botsis 1997	Random, open-label, parallel group.	72	24 weeks	Women with atrophic vaginitis. One women experienced vaginal bleeding with tibolone.
<b>HRT-controlled —oestradiol plus norethisterone acetate</b>				
<i>Modelska and Cummings (2002)</i>				
Hammar 1998	Random, double-blind,	195 (>53)	48 weeks	Bleeding occurred in 34% of subjects on tibolone and 58% on E2/NETA ( $P < 0.0001$ ).
Winkler 2000	Random, double-blind,	60 (45-70)	24 weeks	Bleeding occurred in 25% of subjects on tibolone and 50% of participants on E2/NETA
<i>Moore (1999) a</i>				
Larsson-Cohn 1996	Random, double-blind, parallel	315 (>53)	48 weeks	Less bleeding and spotting with tibolone. Withdrawals for bleeding 2% with tibolone and 12% with E2/NETA.
Habiba 1996	Random, open-label, parallel group.	236 (38-66)	48 weeks (12 weeks analysis of bleeding)	No bleeding/spotting in 85% of tibolone patients and 80% E2/NETA patients after 3 months.

\*Modified from *Modelska and Cummings (2002)* and *Moore (1999)*.

Abbreviations: E2, oestradiol; NETA, norethisterone acetate.

<sup>a</sup> Results from non-randomised studies included in the Moore review have not been shown here.

## Original studies

Six original studies examining the effect of tibolone on vaginal bleeding have been published since the literature searches conducted for the existing systematic reviews outlined above. A summary of the quality and characteristics of these RCTs is shown in Table 179. For further details see Appendix B (Section 9.3).

TABLE 179 TIBOLONE: BLEEDING — ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
Placebo-controlled					
Landgren <i>et al.</i> (2002)	RCT, double-blind <b>Good</b>	Postmenopausal women Intact uterus Experiencing vasomotor symptoms 40-60 years N=775	Tibolone Oral 0.625, 1.25, 2.5 and 5.0 mg N=632	Placebo N=143	Vaginal bleeding or spotting
Meeuwssen <i>et al.</i> (2002)	RCT, double-blind <b>Fair</b>	Postmenopausal women Natural menopause Mean age 54.2 N=85 <sup>a</sup>	Oral Tibolone 2.5 mg N=39	Placebo N=42	Vaginal bleeding or spotting
HRT-controlled					
Baracat <i>et al.</i> (2002)	RCT, open-label <b>Fair</b>	Postmenopausal women Natural menopause 45-65 years N=85	Tibolone Oral 2.5 mg N=40	EPRT CEE (0.625 mg/day) plus MPA (5mg/day) N=45	Breakthrough bleeding or spotting
Huber <i>et al.</i> (2002)	RCT <b>Fair</b>	Postmenopausal women ~ 55 years N=426	Tibolone Oral 2.5 mg N=208	EPRT CEE 0.625 mg/day plus MPA 5 mg/day N=216	Vaginal bleeding during cycles 4-6 (primary outcome) and cycles 1-3 and cumulative bleeding rate (secondary outcome)
Mendoza <i>et al.</i> (2002)	RCT, open-label <b>Poor</b>	Postmenopausal women Intact uterus < 60 years N=165	Oral Tibolone 2.5 mg N=55	Transdermal patch of 17-beta oestradiol 50 µg/day for the first 14 days followed by the addition of norethisterone acetate 0.25 µg/day for the second 14 days. N=110	Vaginal bleeding
Roux <i>et al.</i> (2002)	RCT, double-blind <b>Fair</b>	Postmenopausal women ~ 54 years N=225	Oral Tibolone 1.25, 2.5 mg N=151	Oestradiol 2mg plus norethindrone acetate 1 mg/day N=74	Vaginal bleeding

See Section 9.3.

Abbreviations: CEE, conjugated equine oestrogen; EPRT, oestrogen + progestogen therapy; MPA, medroxyprogesterone acetate; RCT, randomised controlled trial.

Of the six identified studies, the results of the Mendoza *et al.* (2002) study were excluded due to poor methodological quality of the study and the results of the Landgren study were not in a form that was usable for this review although the result will be discussed. The analysis of bleeding in the Huber *et al.* (2002) study was considered to be of fair methodological quality, compared to other outcomes for which the quality of the study was considered poor.

The results of three of the included studies are summarised in Table 180 and Figure 78. These studies show that while bleeding does occur during use of tibolone (Meeuwssen *et al.*, 2002), it is significantly less when compared with the bleeding that occurs with combined continuous HRT regimens (Huber *et al.*, 2002; Roux *et al.*, 2002). The cumulative rate of bleeding was examined in the Huber trial. The results of this analysis, shown in Figure 79, suggest that the majority of bleeding episodes occur in the first 1-3 cycles of therapy, with rates reducing significantly for subsequent cycles.

The results of the Landgren study suggest that 2.5 mg tibolone causes a little more bleeding than placebo although this does not appear to be significant.

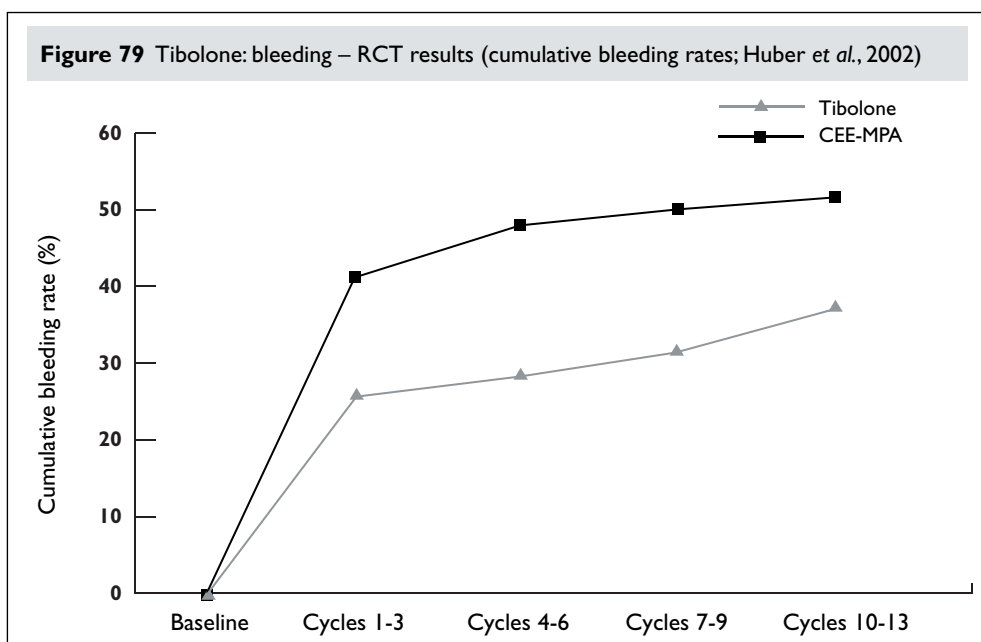
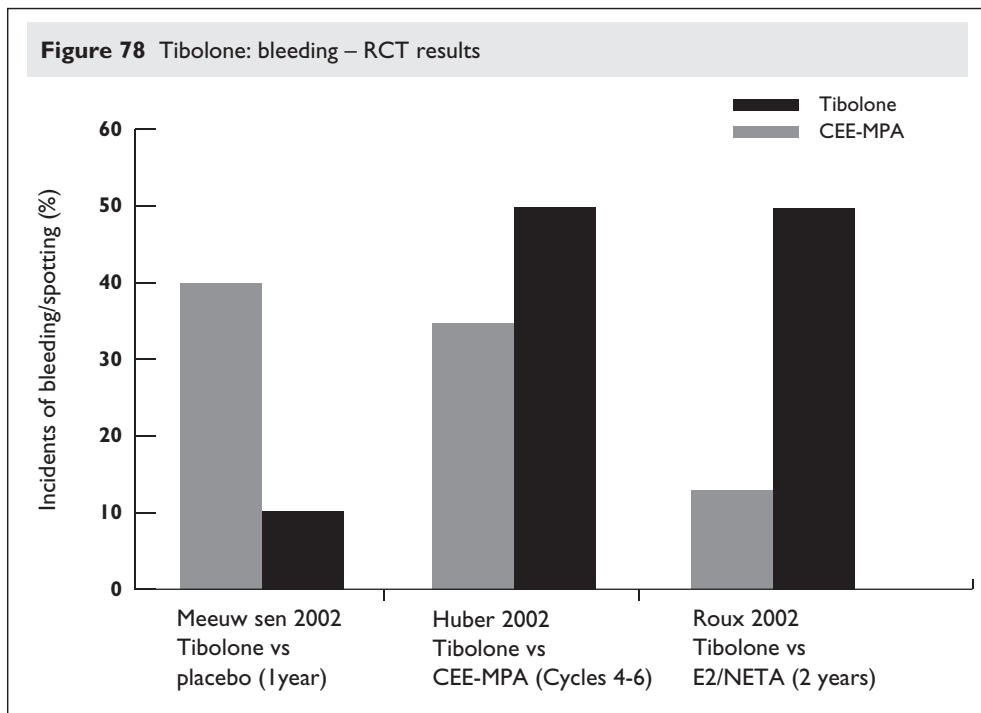
Finally, in a comparison of tibolone versus combined conjugated equine oestrogens plus medroxyprogesterone acetate conducted by Baracat *et al.* (2002), there was no statistically significant difference in breakthrough bleeding/spotting between the two treatments during the 13 cycles of the study (with the exception of one cycle). During cycle 2, significantly more women reported bleeding in the combined HRT arm (44%) compared with the tibolone arm (15%). By the end of the study the bleeding rate was similarly low in both arms (approximately 5-10%). However, in agreement with the results of the Huber study, there does appear to be more bleeding in the combined HRT arm of the study compared with the tibolone arm during the early months of treatment (cycles 1-4).

TABLE 180 TIBOLONE: BLEEDING — RCT RESULTS

Study	Outcome	Duration	Treatment	Control	P value
Meeuwssen 2002	Bleeding/spotting	1 year	<i>Tibolone</i>	<i>Placebo</i>	nr
			16/39	4/42	
Huber 2002	Vaginal bleeding	Cycles 4-6	<i>Tibolone</i>	<i>CEE-MPA</i>	0.004
			31/217	57/212	
Roux 2002 <sup>a</sup>	Vaginal bleeding	2 years	<i>Tibolone</i>	<i>E2/NETA</i>	nr
			9/75	25/74	

*Abbreviations:* CEE, conjugated equine oestrogens; E2, oestradiol; MPA, medroxyprogesterone acetate; nr, not reported; NETA, norethindrone acetate.

<sup>a</sup> It should be noted that 12 subjects in the tibolone 2.5 mg arm were removed from the study at 6 months by an endocrinologist due to lipid/glucose changes. However, as shown below in Figure 79, the majority of cases of bleeding occur within the first 6 months of therapy.



The results of the more recent studies concur with those of the existing systematic reviews, suggesting that while tibolone does cause bleeding, particularly in the early stages of treatment, it is less than that experienced by women using continuous combined HRT.

## Weight gain

### Existing systematic reviews

There were no existing systematic reviews which examined the effect of tibolone on weight gain in postmenopausal women.

### Original studies

No original studies were identified that systematically measured weight gain as an a priori outcome, rather than relying on self-report of weight gain as an adverse event.

## Other unwanted side effects

### Existing systematic reviews

The literature searched identified one systematic review which examined adverse events. The characteristics and quality of this review are summarised in Table 181. For further details see Appendix B (Section 9.3).

TABLE 181 TIBOLONE: OTHER UNWANTED SIDE EFFECTS — EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population No. of studies	Intervention	Comparator	Outcomes
Level I evidence					
Modelska & Cummings (2002)	Systematic review of RCTs (2) <i>Good</i>	Postmenopausal women	Tibolone Oral 2.5 mg	Placebo or HRT	Adverse events

See Section 9.3.

Abbreviations: RCT, randomised controlled trial.

The authors of the review stated that the adverse effects of tibolone versus placebo had not been examined in the RCTs identified by their literature search. They stated that two RCTs comparing tibolone to HRT had examined adverse events, however the results of these are not reported.

## Original studies

Three RCTs have been published since the literature search conducted by Modelska and Cummings which have examined adverse events associated with use of tibolone; both of these were HRT-controlled. The main characteristics and quality of these RCTs are summarised in Table 182. For further details see Appendix B (Section 9.3).

TABLE 182 TIBOLONE: OTHER UNWANTED SIDE EFFECTS — ORIGINAL STUDIES

Study	Study type Study quality	Population N	Dosage	Comparator	Outcomes
Level II evidence					
Baracat <i>et al.</i> (2002)	RCT, open-label <b>Fair</b>	Postmenopausal women Natural menopause 45-65 years N=85	Tibolone Oral 2.5 mg N=40	EPRT CEE (0.625 mg/day) plus MPA (5mg/day) N=45	Adverse events, vital signs and weight were recorded during follow-up visits (only the most commonly reported are shown)
Huber <i>et al.</i> (2002)	RCT <b>Fair</b>	Postmenopausal women ~ 55 years N=426	Tibolone Oral 2.5 mg N=208	EPRT CEE 0.625 mg/day plus MPA 5 mg/day N=216	Adverse events recorded at each visit (only reported for those occurring in ≥ 2.5% of subjects)
Roux <i>et al.</i> (2002)	RCT, double-blind <b>Fair</b>	Postmenopausal women ~ 54 years N=225	Oral Tibolone 1.25, 2.5 mg N=151	Oestradiol 2mg plus norethindrone acetate 1 mg/day N=74	Adverse events recorded at each visit (only reported for those occurring in ≥ 10% of subjects)

See Section 9.3.

Abbreviations: CEE, conjugated equine oestrogen, EPRT, oestrogen + progestogen therapy; MPA, medroxyprogesterone acetate; RCT, randomised controlled trial.

The results of the three included RCTs relating to the other adverse events to be addressed in this review are summarised in Table 183. Due to the selected reporting of commonly occurring adverse events in the trials, data was available for only headache (from the Baracat and Huber studies) and breast pain/tenderness (from all three studies). The results suggest that the occurrence of headaches is similar between tibolone and continuous EPRT (CEE-MPA). On the other hand, breast pain/tenderness is more often associated with EPRT than tibolone, although this is not statistically significant for Baracat *et al.* (2002).

TABLE 183 TIBOLONE: OTHER UNWANTED SIDE EFFECTS — RCT RESULTS

Study	Duration	Tibolone n/N (%)	HRT <sup>a</sup> n/N (%)	P value
<i>Migraine/headache</i>				
Baracat 2002	1 year	4/40 (10.0)	3/45 (6.7)	ns
Huber 2002	1 year	22/250 (8.8)	17/251 (6.8)	ns
Roux 2002	2 years	nr	nr	-
<i>Nausea/vomiting</i>				
Huber 2002	1 year	nr	nr	-
Roux 2002	2 years	nr	nr	-
<i>Breast pain/tenderness</i>				
Baracat 2002	1 year	1/40 (2.5)	5/45 (11.1)	ns
Huber 2002	1 year	6/250 (2.4)	43 (17.1)	< 0.0002
Roux 2002	2 years	2/75 (2.7)	17/74 (23.0)	nr
<i>Fluid retention</i>				
Huber 2002	1 year	nr	nr	-
Roux 2002	2 years	nr	nr	-
<i>Hair loss/gain</i>				
Huber 2002	1 year	nr	nr	-
Roux 2002	2 years	nr	nr	-

Abbreviations: nr, not reported; ns, not significant.

<sup>a</sup> Both trials used continuous EPRT as a comparator. The comparator for the Huber *et al.*(2002) trial was conjugated equine oestrogens plus medroxyprogesterone acetate and for the Roux *et al.*(2002) trial was oestradiol plus norethindrone acetate.

### 3.3 RALOXIFENE

#### **Summary**

There is level II evidence in osteoporotic women that raloxifene decreases the risk of new vertebral fractures, but has no effect on the risk of non-vertebral fractures.

While the risks associated with raloxifene were not specifically examined by this review, there is some level II evidence that raloxifene decreases the risk of breast cancer, and decreases the risk of cardiovascular events in women with existing increased cardiovascular risk, but has no effect on cardiovascular event rates in women in general. There is level II evidence that raloxifene does not alter the risk of endometrial cancer, but that it does significantly increase the risk of VTE. Raloxifene does not appear to increase vaginal bleeding.

#### 3.3.1 OTHER HEALTH BENEFITS

##### **Osteoporotic fracture**

##### **Existing systematic reviews**

Five systematic reviews which examined raloxifene and its effectiveness in the prevention or treatment of postmenopausal osteoporotic fracture were identified by the literature search. All were limited to RCTs and therefore constituted level I evidence. Whilst three of these reviews also reported evidence regarding BMD, the current review only presents the results for fracture as the most patient relevant outcome. The main characteristics and quality of these reviews are summarised in Table 46. For further details see Appendix B (Section 9.2.1).

TABLE 184 RALOXIFENE: OSTEOPOROTIC FRACTURE — EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
Hauselmann & Rizzoli (2003)	Systematic review of RCTs (1) <b>Fair</b>	Postmenopausal women with low bone mass of existing vertebral fracture 60-71 years of age	Raloxifene (also includes others) Oral Any dose	Placebo	Morphometrically determined new vertebral fracture
Miller (2003)	Systematic review - type of study not specified but appears to be limited to RCTs (1) <b>Poor</b>	Adults with postmenopausal or glucocorticoid-induced osteoporosis	Raloxifene (also includes alendronate and risedronate) Oral Any dose	Not stated but raloxifene study is placebo-controlled	1-year vertebral fracture risk
Boyack <i>et al.</i> (2002)	Systematic review of RCTs > 6 months duration (2) <b>Good</b>	Postmenopausal women 54-66 years	Raloxifene Oral Any dose	Placebo or HRT <sup>a</sup>	Fracture
Cranney <i>et al.</i> (2002)	Systematic review of RCTs at least 1-year duration (2) <b>Good</b>	Postmenopausal women	Oral Raloxifene Any dose	Placebo	Vertebral and non-vertebral fracture
Kanis <i>et al.</i> (2002)	Systematic review of RCTs (2) <b>Good</b>	Osteopaenic or osteoporotic women	Raloxifene Any dose	Placebo (with or without calcium or vitamin D)	Fracture

See Section 9.2.1.

Abbreviations: RCT, randomised controlled trial.

<sup>a</sup> No trials measuring fracture as an outcome had HRT as a comparator.

The systematic reviews conducted by Boyack *et al.* (2002), Cranney *et al.* (2002) and Kanis *et al.* (2002) were considered to be of good methodological quality. The search also identified a review considered to be of fair quality (Hauselmann and Rizzoli, 2003), due to its limited search strategy.

The final review by Miller (2002) was considered to be of poor methodological quality. Despite using reasonable systematic review methodology the review only examined 1-year vertebral fracture risk and as such for raloxifene included only one abstract presenting a post-hoc analysis of the extensively published Multiple Outcomes of Raloxifene Evaluation (MORE) study. The 1-year data from this study has subsequently been fully published and will be considered in the next section.

The conclusions reached by these systematic reviews were based on data from only two RCTs: the large MORE study (Ettinger *et al.*, 1999) and a much smaller study by Lufkin *et al.* (1998). As only two studies were included in these reviews, the two available studies will be directly considered. Both of these studies compared raloxifene to placebo.

## Original studies

The literature search identified one RCT which examined the effectiveness of raloxifene in the treatment of established postmenopausal osteoporosis. The MORE study (Ettinger *et al.*, 1999; Delmas *et al.*, 2002) included 7705 women and was three years in duration (although 4-year data has since been published). The characteristics and quality of this study are summarised in Table 185. For further details see Appendix B (Section 9.2.1).

The other available RCT was a small 1-year study by Lufkin *et al.* (1998) which included only 143 women. This study was excluded from our review due to the small sample size (< 50 subjects per arm).

TABLE 185 RALOXIFENE: OSTEOPOROTIC FRACTURE — ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
Ettinger <i>et al.</i> (1999); Delmas <i>et al.</i> (2002)	RCT 3 and 4 years follow-up <sup>a</sup> <b>Fair</b>	Women at least 2 years postmenopausal with established osteoporosis (BMD or prevalent vertebral fracture) Mean age 66 N=7705	Raloxifene Oral 60 mg or 120 mg	Placebo	Radiologically confirmed new vertebral fracture (primary endpoint) Non-vertebral fracture determined by questioning at study visits (secondary outcome)

See Section 9.2.1.

Abbreviations: BMD, bone mineral density; RCT, randomised controlled trial.

<sup>a</sup> During the 4-year follow-up subjects were allowed to take other bone-active agents as indicated. However, results are presented separately for women who did or did not take any.

The results of the 3- and 4-year analyses are presented in Table 186 and Figure 80. Only the 60 mg/day dose of raloxifene is currently approved for use in osteoporotic women in Australia so results relating to the 60 mg arm only are shown where available. With respect to non-vertebral fractures the results were not available individually for the 60 mg and 120 mg dosage arms so the pooled results are presented. The results show that the use of raloxifene in osteoporotic women is associated with a significantly decreased risk of new vertebral fracture. On the other hand, raloxifene had little effect on reducing non-vertebral fracture risk, relative to placebo even when the results are pooled for the 60 and 120 mg doses.

TABLE 186 RALOXIFENE: OSTEOPOROTIC FRACTURE — RCT RESULTS (MORE STUDY)

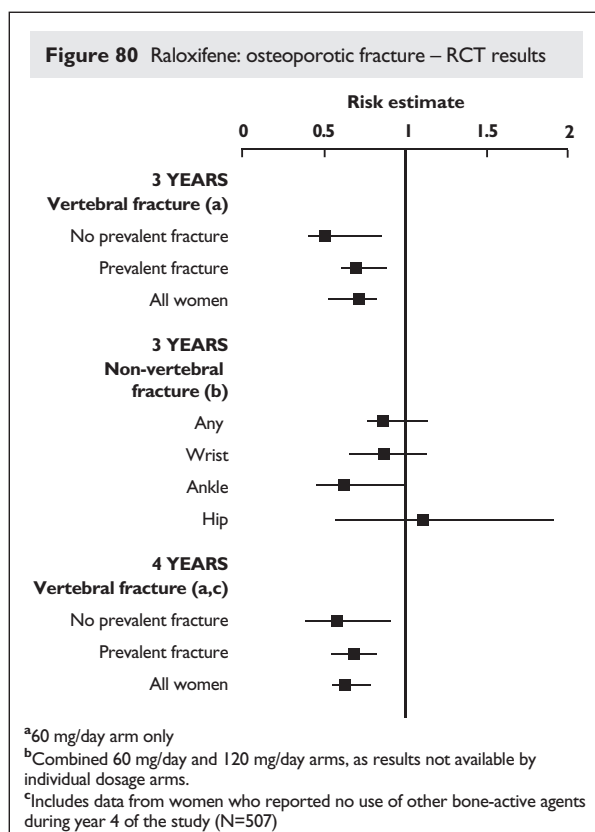
Author	Dosage details	Raloxifene (n/N)	Placebo (n/N)	Type of measure	Risk estimate
<b>3 years<sup>a</sup></b>					
<i>Vertebral fracture</i>					
No prevalent fracture	60 mg/day	35/1490	68/1522	RR	<i>0.5 (0.4, 0.8)</i>
Prevalent fracture	60 mg/day	113/769	163/770	RR	<i>0.7 (0.6, 0.9)</i>
All women	60 mg/day	148/2259	231/2292	RR	<i>0.7 (0.5, 0.8)</i>
<i>Non-vertebral fracture</i>					
Any	60 and 120 mg/day	437/4536	240/2292	RR	0.9 (0.8, 1.1)
Wrist	60 and 120 mg/day	151/4536	86/2292	RR	0.9 (0.6, 1.1)
Ankle	60 and 120 mg/day	34/4536	28/2292	RR	0.6 (0.4, 1.0)
Hip	60 and 120 mg/day	40/4536	18/2292	RR	1.1 (0.6, 1.9)
<b>4 years<sup>b</sup></b>					
<i>Vertebral fracture</i>					
No prevalent fracture	60 mg/day	35/nr	67/nr	RR	<i>0.52 (0.35, 0.78)</i>
Prevalent fracture	60 mg/day	110/nr	158/nr	RR	<i>0.65 (0.52, 0.81)</i>
All women	60 mg/day	145/nr	225/nr	RR	<i>0.63 (0.52, 0.77)</i>

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: nr, not reported; RR, relative risk.

<sup>a</sup> Includes women who completed the study and who had evaluable radiographs at 36 months.

<sup>b</sup> During the 4-year follow-up subjects were allowed to take other bone-active agents as indicated. However, results are presented separately for women who did or did not take any. The results presented here were for women who did not take any other bone-active agents.



### 3.3.2 UNWANTED SIDE EFFECTS AND OTHER HEALTH RISKS

While the majority of literature regarding raloxifene relates to its use as a treatment for postmenopausal osteoporosis (for which it is indicated in Australia), it is also important to consider potential side effects and other health risks. While these outcomes have not been examined systematically as part of this review, they are discussed below.

As part of their good quality systematic review, Boyack *et al.* (2002) examined the side effects and risks associated with raloxifene use. They concluded that raloxifene reduced oestrogen receptor-positive breast cancer, and did not increase the risk of endometrial cancer. On the other hand, raloxifene did increase the risk of VTE.

The majority of the available information regarding the safety of raloxifene has come from detailed analyses of the MORE trial. The main safety findings of this study are summarised below in Table 187 and Table 188.

With regard to the unwanted side effects of raloxifene therapy, vaginal bleeding occurred in a similar proportion of women in the raloxifene and placebo arms (~ 3%). Side effects that occurred more commonly in the raloxifene arms included hot flushes, leg cramps and peripheral oedema.

TABLE 187 RALOXIFENE: UNWANTED SIDE EFFECTS A — MORE STUDY (ETTINGER *ET AL.*, 1999)

Adverse events	Raloxifene 60 mg/d n (%) N=2257	Raloxifene 120 mg/d n (%) N=2572	Placebo n (%) N=2576	P value <sup>b</sup>
Vaginal bleeding	67 (3.4)	56 (2.8)	62 (3.1)	> 0.05
<i>Occurring more often in the raloxifene arms</i>				
Influenza syndrome	346 (13.5)	345 (13.4)	293 (11.4)	0.01
Hot flushes	249 (9.7)	269 (11.6)	165 (6.4)	< 0.001
Leg cramps	178 (7.0)	178 (6.9)	96 (3.7)	< 0.001
Peripheral oedema	134 (5.2)	168 (6.5)	114 (4.4)	< 0.01
Endometrial cavity fluid <sup>c</sup>	60 (8.1)	66 (8.7)	43 (5.7)	0.02
<i>Occurring more often in the placebo arm</i>				
Hypertension	177 (6.9)	194 (7.5)	231 (9.0)	0.01
Hypercholesterolaemia	55 (2.2)	50 (1.9)	121 (4.7)	< 0.001
Haematuria	35 (1.4)	33 (1.3)	55 (2.1)	< 0.01

<sup>a</sup> Adverse events experienced by at least 2% of women in each group and for which the percentages differed significantly between compared with the placebo group. Bleeding has been included also.

<sup>b</sup> Combined raloxifene groups vs placebo

<sup>c</sup> Includes only 2262 women who had ultrasonography.

A number of more detailed analyses of the MORE study have examined the longer-term health risks associated with raloxifene. A selection of the main results is shown in Table 188. These results suggest that raloxifene reduces the risk of cardiovascular disease in women with an existing increased risk of cardiovascular disease, but not when all women are considered in total. The risk of VTE was significantly increased with raloxifene use. Breast cancer risk was decreased in all women, and a subset of women with oestrogen receptor-positive breast cancer. No increase in risk was seen for endometrial cancer.

TABLE 188 RALOXIFENE: OTHER HEALTH RISKS — 'MORE' STUDY

Study	Outcome	Follow-up	Ral 60 mg/d vs placebo	Ral 120 mg/d vs placebo
Barrett-Connor <i>et al.</i> (2002)	Coronary and cerebrovascular events <sup>a</sup> (all women)	4 years	RR 0.86 (0.64, 1.15)	Not relevant
Barrett-Connor <i>et al.</i> (2002)	Coronary and cerebrovascular events <sup>b</sup> (subset of women with increased risk at baseline)	4 years	<i>RR 0.60 (0.38, 0.95) <sup>c</sup></i>	
Cummings <i>et al.</i> (1999)	Venous thromboembolism	40 months	<i>RR 3.1 (1.5, 6.2) <sup>c</sup></i>	
Cummings <i>et al.</i> (1999)	Endometrial cancer	40 months	RR 0.8 (0.2, 2.7) <sup>c</sup>	
Cauley <i>et al.</i> (2001)	Breast cancer (all women)	4 years	<i>RR 0.28 (0.17, 0.46) <sup>c</sup></i>	
Cauley <i>et al.</i> (2001)	Breast cancer (women with E <sub>2</sub> -receptor positive tumours only)	4 years	<i>RR 0.16 (0.09, 0.30) <sup>c</sup></i>	

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: E<sub>2</sub>, oestrogen; RR, relative risk.

<sup>a</sup> Coronary events including myocardial infarction, unstable angina and coronary ischaemia and cerebrovascular events including stroke or transient ischaemic attack.

<sup>b</sup> Cardiovascular risk was determined at study entry by the presence of multiple cardiovascular risk factors or prior coronary events or revascularisation procedure.

<sup>c</sup> Pooled 60 mg and 120 mg results.

### 3.4 SELECTED COMPLEMENTARY AND ALTERNATIVE MEDICINES

#### Summary

There is some conflicting level II evidence that soy and soy products improve vasomotor and urogenital symptoms, and limited level II evidence that soy protein has no effect on sleep disturbances. There is level I evidence that soy and soy products have no significant impact on global menopausal symptom or quality of life scales.

There is level II evidence that red clover (Promensil), dong quai, Evening Primrose oil, ginseng and a Chinese herb mixture have no effect on vasomotor symptoms, and a paucity of good quality evidence regarding the efficacy of black cohosh (Remifemin) against vasomotor symptoms. There is no evidence regarding the effect of these herbs on sleep disturbances, and limited level II evidence that dong quai has no effect on urogenital symptoms.

There is conflicting level II evidence that black cohosh is as efficacious as HRT at relieving menopausal symptoms and improving quality of life. However, there is limited level II evidence that red clover, dong quai, ginseng and a Chinese herb mixture have no significant effect on global menopausal symptom or quality of life scales.

The current review is limited to selected complementary and/or alternative therapies (CAMs) that are commonly marketed and used for the relief of menopausal symptoms in Australia. These include soy and soy products and a number of herbs including red clover and black cohosh.

## 3.4.1 BENEFITS FOR THE RELIEF OF MENOPAUSAL SYMPTOMS

**Vasomotor symptoms****Existing systematic reviews**

Three systematic reviews were identified that examine the efficacy of various CAMs in the treatment of vasomotor symptoms. The characteristics and quality of these reviews are summarised in Table 189. One of these reviews constituted level I evidence and was considered to be of fair methodological quality (Kronenberg and Fugh Berman, 2002). The remaining two reviews were considered to be level I/III-2 evidence as they included all study types. These were considered to be of poor methodological quality due to a lack of information regarding studies included in the review and no quality assessment. These poor quality reviews will not be considered further. For further details see Appendix B (Section 9.4).

TABLE 189 CAM: VASOMOTOR SYMPTOMS — EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
Kronenberg & Fugh-Berman (2002)	Systematic review of RCTs (15) <i>Fair</i>	Postmenopausal women	Soy, soy products, herbs and other therapies (not included) Any mode of administration Any dose	Placebo or active	Vasomotor symptoms
Level I/III-2 evidence					
Tesch (2002)	Systematic review of all studies (unclear; not listed) <i>Poor</i>	Postmenopausal women	Herbs Mode of administration not specified Any dose	Not stated	Not stated
Seidl & Stewart (1998)	Systematic review of all studies including case reports and lay literature (unclear; not listed) <i>Poor</i>	Postmenopausal women	Alternative treatments (includes nutritional supplements, herbs, homeopathic and physical therapy). Mode of administration not specified Any dose	Not stated	Vasomotor symptoms

See Section 9.4.

Abbreviations: RCT, randomised controlled trial.

The results of the review of soy and soy products and their efficacy in reducing vasomotor symptoms in postmenopausal women are summarised in Table 190. In general, the results are inconsistent. Four of the eight studies showed a reduction in the frequency and/or severity of hot flushes/night sweats in women treated with soy or soy products compared with controls while three studies showed no difference. The remaining study (Dalais, 1998) only reported results relative to baseline and showed that the frequency of hot flushes improved from baseline in subjects in the control arm only (linseed and wheatmeal) while there was no change from baseline in subjects in the soy arm. In summary, these results suggest that while soy and soy products show some promise in improving vasomotor symptoms, the evidence available at present fails to prove a consistent effect.

TABLE 190 CAM: VASOMOTOR SYMPTOMS — RESULTS OF EXISTING SYSTEMATIC REVIEWS (SOY AND SOY PRODUCTS)

Study	Included study details	Dose and duration	Outcome and size of effect
<i>Soy and soy extracts</i>			
Kronenberg and Fugh-Berman (2002) <sup>a</sup>	Van Patten 2002 Canada N=157 Breast cancer and hot flushes	Soy beverage (90 mg isoflavones/d) vs rice beverage (control) 3 months	Hot flushes — no difference in frequency between groups (decreased in both; 30% soy, 40% rice).
	St Germain 2001 United States N=91 Perimenopausal with 10 or more hot flushes/d Age 42-62 y	40 g/d isoflavone-rich soy protein vs 40 g/d isoflavone-poor soy protein vs 40 mg/d whey protein (control) 24 weeks	Hot flushes — no significant difference in frequency or severity between groups (decreased in all groups) Night sweats — no significant difference in frequency or severity between groups (decreased in all groups)
	Scambia 2000 Italy N=39 includes surgical and early menopause Age 29-63	Standardised soy extract (50 mg/d isoflavones) vs placebo. Other treatments added after this (not included here) 6 weeks	Hot flushes — significantly decreased frequency and severity for soy vs placebo ( $P<0.001$ and $P<0.0001$ respectively).
	Upmalis 2000 United States N=177 with $\geq 5$ hot flushes/d Age $\geq 50$ y	Standardised soy isoflavone extract (50 mg/d isoflavones) vs placebo. 12 weeks	Hot flushes — frequency reduced at 6 weeks ( $P=0.03$ ) and severity but not frequency reduced at 12 weeks ( $P=0.01$ ) compared with placebo. Night sweats — Severity of night sweats reduced at 12 weeks ( $P=0.01$ ).
	Albertazzi 1998 Italy N=104 with $\geq 7$ hot flushes/d Age 45-62 y	60 g isolated soy protein powder/d (76 mg isoflavones and 40 g protein) vs isoflavone-free casein powder (control) 12 weeks	Hot flushes — significantly decreased frequency at 12 weeks compared with control ( $P<0.001$ )
	Dalais 1998 Australia N=52 with $\geq 14$ hot flushes/w Age 45-65 y	45 g/d soy grits (bread) or linseed and wheatmeal (control) 12 each phase + 4 week washout	Hot flushes — Compared with baseline only linseed and wheatmeal reduced frequency.
	Brzezinski 1997 Israel N=145 peri- and postmenopausal with $\geq 1$ climacteric symptom Age 43-65 y	Phytoestrogen diet containing soybean food and flaxseed (1/4 caloric intake) vs control (normal diet) 12 weeks	Hot flushes — soy diet significantly reduced severity score ( $P=0.004$ ).
	Murkies 1995 Australia N=58 with $> 14$ hot flushes/w Age 30-70 y	45 g/d soy flour vs 45 g/d wheat flour 12 weeks	Hot flushes — No significant difference between groups in frequency of hot flushes or hot flush scores.

<sup>a</sup> One study from this review excluded due to incorrect study population. One study excluded due to crossover design with no washout.

The efficacy of various herbs in treating vasomotor symptoms as reviewed by Kronenberg and Fugh-Berman (2002), is summarised in Table 191. Of the six herbs examined in the Kronenberg review, minimal evidence was available to support the efficacy of these treatments in the reduction of hot flushes and/or night sweats. The only study which showed a benefit was Stoll (1987) which compared black cohosh (Remifemin) with placebo. However, the results of this study showed conjugated oestrogens had no effect on vasomotor symptoms. Given that there is unambiguous evidence that oestrogen is effective in relieving vasomotor symptoms, this unexpected finding calls the benefit shown for black cohosh into question.

TABLE 191 CAM: VASOMOTOR SYMPTOMS — RESULTS OF EXISTING SYSTEMATIC REVIEWS (HERBS)

Study	Included study details	Dose and duration	Outcome and size of effect
<i>Black cohosh (Remifemin)</i>			
Kronenberg and Fugh-Berman (2002) <sup>a</sup>	Stoll 1987 Germany N=80 (41 menopausal) with > 3 hot flushes/d and "psychic complaints" Age 46-58	Remifemin tablets 4 mg bd vs conjugated oestrogens 0.625 mg/d vs placebo 3 months	Decrease in hot flushes greatest with Remifemin (4.9 to 0.7/d) compared with HRT (5.2 to 3.2/d) and placebo (5.1 to 3.1/d) Note: lack of effect with HRT is not expected given known efficacy of HRT in relieving hot flushes.
<i>Red clover (Promensil)</i>			
Kronenberg and Fugh-Berman (2002)	Baber 1999 Australia N=51 > 3 hot flushes/d Aged ≥ 40 y	Promensil 40 mg total isoflavones vs placebo 3 months	Hot flushes — no difference in frequency between groups (decreased in both).
	Knight 1999 Australia N=37 > 3 hot flushes/d Aged 40-65	Promensil 40 mg total isoflavones vs Promensil 160 mg total isoflavones vs placebo 3 months	Hot flushes — no difference in frequency between groups (decreased in all groups).
<i>Dong quai</i>			
Kronenberg and Fugh-Berman (2002)	Hirata 1997 United States N=71 with > 14 hot flushes/w (any severity) or > 5 moderate-severe hot flushes/w Age 45-69	Dong quai 3 capsules td vs placebo 3 months	Hot flushes — No difference between groups in number of hot flushes Note: Dong quai not considered oestrogenic and not usually prescribed alone in Chinese Medicine
<i>Evening primrose oil</i>			
Kronenberg and Fugh-Berman (2002)	Chenoy 1994 United Kingdom N=56 with > 3 hot flushes/d Age 45-67	2000 mg evening primrose oil with 20 mf vitamin E bd vs placebo 6 months	Hot flushes — daytime hot flushes decreased in placebo group only. Night-time hot flushes decreased in both groups.
<i>Ginseng</i>			
Kronenberg and Fugh-Berman (2002)	Wiklund 1999 Sweden N=384 with ≥ 6 hot flushes during 3 of 7 days Age 45-65 y	Ginseng (100 mg of standardised extract) vs placebo 2 months	Hot flushes — No significant differences between groups (assessed as part of WHQ).
<i>Chinese herb mixture</i>			
Kronenberg and Fugh-Berman (2002)	Davis 2001 Australia N=78 with ≥ 14 hot flushes or night sweats/w	Chinese herbal formula (12 herbs) vs bitter placebo 3 months	Hot flushes and night sweats — no difference in frequency between groups.

Abbreviations: WHQ, Women's Health Questionnaire.

## Original studies

Three RCTs have been published since the Kronenberg review which provide data regarding the efficacy of soy or soy products at reducing vasomotor symptoms. One of these studies (by Faure *et al.*, 2002) is considered to be of good methodological quality and the other is considered to be of fair methodological quality (Penotti *et al.*, 2003). The final study, by Sammartino *et al.* (2003) is considered to be of poor methodological quality and will not be considered further.

The main characteristics and quality of the two remaining included studies are summarised in Table 192. For further details see Appendix B (Section 9.4).

TABLE 192 CAM: VASOMOTOR SYMPTOMS — ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
Penotti <i>et al.</i> (2003)	Double-blind RCT 6 months <i>Fair</i>	Postmenopausal women aged 45-60 years At least 7 hot flushes per day in preceding 15 days. Mean age 52 N=62	Oral tablet containing 36 mg soy-derived isoflavones (5.5 mg of genisteine, 18 mg daidzeine and 12.5 mg glyciteine). 2 tablets/day N=28	Matching placebo N=34	Daily hot flushes
Faure <i>et al.</i> (2002)	RCT 4 months <i>Good</i>	Postmenopausal women with 7 or more moderate to severe hot flushes per day during 2 weeks before study Mean age ~ 53.5 N=75	Oral 325 mg capsule standardised isoflavone supplement prepared from soy extract (Phytosoya). N=39	Placebo N=36	Vasomotor symptoms (number and responders)

See Section 9.4.

Abbreviations: RCT, randomised controlled trial.

The results of the study by Penotti *et al.* (2002) are summarised in Table 193. These results show that over the six months of the study, hot flushes were reduced in both the isoflavone and placebo arms; there was no significant difference in the mean number of hot flushes between the two study arms at any time-point during the study. It should be noted that this analysis was carried out on evaluable patients only with patients dropping out of the study excluded from the analysis. However, given that the number of dropouts is similar between the isoflavone and placebo arms (6/28 in the isoflavone arm and 7/34 in the placebo arm), it is unlikely that this would bias the results in favour of either group.

TABLE 193 CAM: VASOMOTOR SYMPTOMS — RCT RESULTS  
(EVALUABLE PATIENT RESULTS; (PENOTTI *ET AL.*, 2002)

	Isoflavone		Placebo	
	Number of patients	Mean number (SD) hot flushes	Number of patients	Mean number (SD) hot flushes
Baseline	28	9.9 (4.5)	34	8.6 (2.9)
Month 1	28	6.1 (4.0)	34	5.3 (3.3)
Month 2	27	5.8 (4.1)	33	4.5 (3.7)
Month 3	24	5.5 (3.8)	29	4.0 (3.7)
Month 4	23	5.2 (4.0)	29	4.3 (3.7)
Month 5	22	5.4 (4.3)	27	4.1 (3.7)
Month 6	22	4.6 (3.8)	27	4.0 (3.9)

Abbreviations: SD, standard deviation.

Table 194 shows the results of the ITT analysis of vasomotor symptom reduction (Faure *et al.*, 2002). The results of this 'last observation carried forward' analysis show that the soy extract (Phytosoya) significantly reduces the frequency of hot flushes compared with placebo during 16 weeks of treatment. However, it should be noted that there were substantial differences between withdrawals from the study in the placebo group compared with the Phytosoya group (14 vs 6). A per protocol analysis including only data observed at the 16 week endpoint showed no difference between the two groups. However, an analysis of subjects who 'responded' to treatment showed that more than twice as many subjects on Phytosoya responded compared with placebo.

TABLE 194 CAM: VASOMOTOR SYMPTOMS — RCT RESULTS  
(INTENTION-TO-TREAT ANALYSIS; FAURE *ET AL.*, 2002)

	Phytosoya	Placebo	P value
	Mean (SD)	Mean (SD)	
Baseline	10.1 (6.4)	9.4 (3.4)	ns
	Mean change from baseline (SEM)	Mean change from baseline (SEM)	
Week 4	-4.2 (0.8)	-2.2 (0.8)	-
Week 8	-5.6 (0.9)	-2.7 (0.7)	-
Week 16	-6.4 (1.0)	-2.2 (1.2)	0.01 <sup>a</sup>
	%	%	
Responders <sup>b</sup>	65.8%	32.4%	nr

Abbreviations: nr, not reported; ns, not significant; SD, standard deviation; SEM, standard error of the mean.

<sup>a</sup> ITT LOCF repeated measures model — treatment effect. All time effect and treatment \* time effect models were non significant.

<sup>b</sup> ≥ 50% reduction in number of hot flushes from baseline.

The results of the Faure study add to those included in the Kronenberg *et al.* (2002) review, which suggest that soy or soy products may be effective in alleviating menopausal symptoms. However, the results of the Penotti study showed no benefit.

## Urogenital symptoms/sexual dysfunction

### Existing systematic reviews

One review was identified which examined the effect of CAM on urogenital and sexual symptoms of menopause. This review, by Kronenberg and Fugh-Berman (2002) was considered to be of fair methodological quality. The main characteristics and quality of this review are summarised in Table 195. For further details see Appendix B (Section 9.4).

TABLE 195 CAM: UROGENITAL SYMPTOMS/SEXUAL DYSFUNCTION — EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
Kronenberg & Fugh-Berman (2002)	Systematic review of RCTs (3) <i>Fair</i>	Postmenopausal women	Soy, soy products, herbs of other therapies (not included) Any mode of administration Any dose	Placebo or active	Vaginal dryness

See Section 9.4.

Abbreviations: RCT, randomised controlled trial.

The results of the systematic review of soy and soy products in relation to improvement of vaginal dryness are summarised in Table 196. The results are inconsistent as one study showed no significant difference between soy protein (isoflavone-rich) and control (whey protein which is isoflavone-poor) while the other showed a diet high in phytoestrogens significantly improved vaginal dryness compared with a normal diet.

TABLE 196 CAM: UROGENITAL SYMPTOMS — EXISTING SYSTEMATIC REVIEW RESULTS (SOY AND SOY PRODUCTS)

Study	Included study details	Dose and duration	Outcome and size of effect
Soy and soy extracts			
Kronenberg and Fugh-Berman (2002) <sup>a</sup>	St Germain 2001 United States N=91 Perimenopausal with 10 or more hot flushes/d Age 42-62 y	40 g/d isoflavone-rich soy protein vs 40 g/d isoflavone-poor soy protein vs 40 mg/d whey protein (control) 24 weeks	Vaginal dryness — No significant difference between groups
	Brzezinski 1997 Israel N=145 peri- and postmenopausal with ≥ 1 climacteric symptom Age 43-65 y	Phytoestrogen diet containing soybean food and flaxseed (1/4 caloric intake) vs control (normal diet) 12 weeks	Vaginal dryness — Soy diet significantly decreased symptoms (P=0005)

One study examined the efficacy of the herb dong quai compared with placebo in improving vaginal dryness in postmenopausal women. This study showed no difference between the two groups. The authors of the review note that dong quai is not considered oestrogenic and is usually not prescribed alone in Chinese medicine.

TABLE 197 CAM: UROGENITAL SYMPTOMS — EXISTING SYSTEMATIC REVIEW RESULTS (HERBS)

Study	Included study details	Dose and duration	Outcome and size of effect
<i>Dong quai</i>			
Kronenberg and Fugh-Berman (2002)	Hirata 1997 United States N=71 with > 14 hot flushes/w (any severity) or > 5 moderate-severe hot flushes/w Age 45-69	Dong quai 3 capsules td vs placebo 3 months	Vaginal dryness — No significant difference between groups Note: Dong quai not considered oestrogenic and not usually prescribed alone in Chinese Medicine

### Original studies

No original studies published since the Kronenberg review specifically examined the effect of CAMs upon urogenital or sexual symptoms.

### Sleep disturbances

#### Existing systematic reviews

One review was identified which examined the benefits of CAM in improving sleep disturbances in postmenopausal women (Kronenberg and Fugh-Berman, 2002). This review was considered to be of fair methodological quality, and is summarised in Table 198. For further details see Appendix B (Section 9.4).

TABLE 198 CAM: SLEEP DISTURBANCES — EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
Kronenberg & Fugh-Berman (2002)	Systematic review of RCTs (1) <i>Fair</i>	Postmenopausal women	Soy, soy products, herbs of other therapies (not included) Mode of administration not specified Any dose	Placebo or active	Insomnia

See Section 9.4.

Abbreviations: RCT, randomised controlled trial.

The results of this review are summarised in Table 199. One study was identified which examined the efficacy of an isoflavone-rich soy protein in reducing insomnia. This study showed no difference between the soy protein and the control (an isoflavone-poor whey protein).

TABLE 199 CAM: SLEEP DISTURBANCES — EXISTING SYSTEMATIC REVIEW RESULTS (SOY AND SOY PRODUCTS)

Study	Included study details	Dose and duration	Outcome and size of effect
<i>Soy and soy extracts</i>			
Kronenberg and Fugh-Berman (2002) <sup>a</sup>	St Germain 2001 United States N=91 Perimenopausal with 10 or more hot flushes/d Age 42-62 y	40 g/d isoflavone-rich soy protein vs 40 g/d isoflavone-poor soy protein vs 40 mg/d whey protein (control) 24 weeks	Insomnia — no significant differences between groups.

<sup>a</sup> One study excluded due to crossover design with no washout.

### Original studies

No original studies published since the Kronenberg review specifically examined the effect of CAMs upon sleep disturbance. However, one study did include insomnia in a global menopause symptom scale (Han *et al.*, 2002). For further details see the section on Global Menopause Scales and Quality of Life.

## Global menopause symptom and quality of life scales

### Existing systematic reviews

Two existing systematic reviews were identified which examined the efficacy of CAM in improving global menopausal symptom scores or quality of life. The main characteristic and quality of the two included reviews are summarised in Table 200. For further details see Appendix B (Section 9.4).

TABLE 200 CAM: GLOBAL MENOPAUSAL SYMPTOM AND QOL SCALES — EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
(Borrelli & Ernst 2002)	Systematic review of RCTs (4, + animal and <i>in vitro</i> studies) <b>Good</b>	Postmenopausal women	Black cohosh Mode of administration and dose not specified	Placebo or active	Any (including menopausal symptoms)
(Kronenberg & Fugh-Berman 2002)	Systematic review of RCTs (13) <b>Fair</b>	Postmenopausal women	Soy, soy products, herbs of other therapies (not included) Any mode of administration or dose	Placebo or active	Menopausal symptoms

See Section 9.4.

Abbreviations: RCT, randomised controlled trial.

One review (Kronenberg and Fugh-Berman, 2002) looked at soy and soy products and their effect on menopausal symptoms (four studies) and quality of life (one study). All five studies showed no significant difference between treatment and control. These results are summarised in Table 201.

TABLE 201 CAM: GLOBAL MENOPAUSAL SYMPTOM AND QOL SCALES EXISTING SYSTEMATIC REVIEW RESULTS — (SOY AND SOY PRODUCTS)

Study	Included study details	Dose and duration	Outcome and size of effect
<i>Soy and soy extracts</i>			
Kronenberg and Fugh-Berman (2002) <sup>a</sup>	Han 2002 Brazil N=82 with hot flushes Age 45-55	Capsules containing 150.9 mg soy protein and 100 mg isoflavones vs placebo 4 months	Kupperman Index — no difference between groups
	Scambia 2000 Italy N=39 includes surgical and early menopause Age 29-63	Standardised soy extract (50 mg/d isoflavones) vs placebo. Other treatments added after this (not included here) 6 weeks	Greene menopause scale — no difference between groups
	Upmalis 2000 United States N=177 with ≥ 5 hot flushes/d Age ≥ 50 y	Standardised soy isoflavone extract (50 mg/d isoflavones) vs placebo. 12 weeks	QoL — no significant difference
	Albertazzi 1998 Italy N=104 with ≥ 7 hot flushes/d Age 45-62 y	60 g isolated soy protein powder/d (76 mg isoflavones and 40 g protein) vs isoflavone-free casein powder (control) 12 weeks	Kupperman Index — no difference between group
	Brzezinski 1997 Israel N=145 peri and postmenopausal with ≥ 1 climacteric symptom Age 43-65 y	Phytoestrogen-rich diet containing soybean food and flaxseed (1/4 caloric intake) vs control 12 weeks	Menopause symptom questionnaire — no significant difference between groups

<sup>a</sup> One study excluded from this review due to incorrect study population. One study excluded due to crossover design with no washout.

Table 202 summarises the results of the two systematic reviews which have examined the efficacy of various herbs in improving quality of life. The results of the two systematic reviews suggest that black cohosh is as efficacious as HRT at relieving menopausal symptoms and improving quality of life. One study showed that black cohosh was significantly more efficacious than placebo however this study also showed no effect of HRT, which is an unexpected finding. Other herbs including red clover (Promensil), dong quai, ginseng and a Chinese herb mixture were not significantly better than placebo in reducing menopausal symptoms or quality of life.

TABLE 202 CAM: GLOBAL MENOPAUSAL SYMPTOM AND QOL SCALES — EXISTING SYSTEMATIC REVIEW RESULTS (HERBS)

Study	Included study details	Dose and duration	Outcome and size of effect
<i>Black cohosh (Remifemin)</i>			
Borrelli & Ernst (2002) <sup>a</sup>	Warnecke 1985 N=60 menopausal women	Remifemin liquid (40 drops bd) vs conjugated oestrogens 0.25 mg/d vs diazepam 2mg/d 3 months	Kupperman Index, Hamilton Anxiety Scale, Self-assessment Depression Scale, and Clinical Global Impression scale — improved with Remifemin and CE
	Stoll 1987 N=80 with climacteric complaints	Remifemin tablets 4 mg bd vs conjugated oestrogens 0.625 mg/d vs placebo 3 months	Kupperman Index and Hamilton anxiety scale — improved all parameters compared with placebo. Note: Lack of effect with oestrogen
	Lehmann-Willenbrock 1988 N=60 with hysterectomy and at least 1 ovary	Remifemin tablets (4 mg of triterpene glycosides bd) vs oestriol 1 mg/d vs conjugated oestrogens 1.25 mg/d vs oestrogen/progestogen	Kupperman Index — improved in all groups, no difference between groups.
Kronenberg and Fugh-Berman (2002) <sup>a</sup>	Warnecke 1985 Germany N=60 (48 menopausal) with menopausal symptoms Age 45-60 y	Remifemin liquid (40 drops bd) vs conjugated oestrogens 0.25 mg/d vs diazepam 2mg/d 3 months	Kupperman Index, Hamilton Anxiety Scale, Self-assessment Depression Scale, and Clinical Global Impression scale — highly significant reductions with all three treatments Note: no statistical calculations reported.
	Stoll 1987 Germany N=80 (41 menopausal) with > 3 hot flushes/d and "psychic complaints" Age 46-58	Remifemin tablets 4 mg bd vs conjugated oestrogens 0.625 mg/d vs placebo 3 months	Kupperman Index — Significant improvement in Remifemin arm but not placebo or oestrogen arms. Note: Lack of effect with oestrogen findings calls other results into question.
	Lehmann-Willenbrock 1988 Germany N=60 (41 menopausal) with hysterectomy and at least 1 ovary Age ≥ 40 y	Remifemin tablets (4 mg of triterpene glycosides bd) vs oestriol 1 mg/d vs conjugated oestrogens 1.25 mg/d vs oestrogen/progestogen	Kupperman Index — improved in all groups, no difference between groups.

Study	Included study details	Dose and duration	Outcome and size of effect
<i>Red clover(Pro mensil)</i>			
Kronenberg and Fugh-Berman (2002)	Baber 1999 Australia N=51 > 3 hot flushes/d Aged $\geq$ 40 y	Promensil 40 mg total isoflavones vs placebo 3 months	Greene menopause scale — no difference between groups.
	Knight 1999 Australia N=37 > 3 hot flushes/d Aged 40-65	Promensil 40 mg total isoflavones vs Promensil 160 mg total isoflavones vs placebo 3 months	Greene menopause scale — no difference between groups.
<i>Dong quai</i>			
Kronenberg and Fugh-Berman (2002)	Hirata 1997 United States N=71 with > 14 hot flushes/w(any severity) or > 5 moderate-severe hot flushes/w Age 45-69	Dong quai 3 capsules td vs placebo 3 months	Kupperman Index — both decreased, no difference between groups.
<i>Ginseng</i>			
Kronenberg and Fugh-Berman (2002)	Wiklund 1999 Sweden N=384 with $\geq$ 6 hot flushes during 3 of 7 days Age 45-65 y	Ginseng (100 mg of standardised extract) vs placebo 2 months	Psychological well-being Index and Women's Health Questionnaire — no significant difference between groups.
<i>Chinese herb mixture</i>			
Kronenberg and Fugh-Berman (2002)	Davis 2001 Australia N=78 with $\geq$ 14 hot flushes or night sweats/w	Chinese herbal formula (12 herbs) vs bitter placebo 3 months	Menopause-Specific Quality of Life Questionnaire score — decrease in both groups, no difference between groups.

<sup>a</sup> One study excluded due to large proportion of non-menopausal women.

## Original studies

Three studies which examine the effect of soy isoflavones on global menopause symptoms, have been published since the Kronenberg *et al.* (2002) review (two on soy isoflavones and one on black cohosh). None of the studies had at least 50 patients in each arm.

The main characteristics and quality of these studies are summarised in Table 203. The study by Sammartino *et al.* (2003) is considered to be of poor methodological quality so it will not be considered in detail. For further details see Appendix B (Section 9.4).

TABLE 203 CAM: GLOBAL MENOPAUSE SYMPTOM AND QOL SCALES — ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
<i>Soy and/or soy products</i>					
Sammartino <i>et al.</i> (2003)	Double-blind RCT 12 28-day cycles <b>Poor</b>	Postmenopausal women with at least 7 moderate-severe hot flushes/day in the 2 weeks preceding Mean age 52 N=70	36 mg/day oral genisteine (Fitogen) 2 tablets/day N=35	Calcium supplements N=35	Climacteric symptoms as measured by the Kupperman Index.
Han <i>et al.</i> (2002)	Double-blind RCT 4 months <b>Good</b>	Postmenopausal women aged 45-55 with an intact uterus. Presence of hot flushes. N=82	Oral capsule containing 50.3 mg soy protein and 33.3 mg isoflavone. N=40	Matching placebo N=40	Change in Kupperman Index scores from baseline to post-treatment.
<i>Black cohosh</i>					
Wuttke <i>et al.</i> (2003)	Double-blind RCT 3 months <b>Fair</b>	Postmenopausal women aged 40-60 years N=62	Black cohosh extract (40 mg/d) 2 capsules/d N=20	Placebo N=20 Conjugated oestrogens N=22	Change from baseline Menopause Rating Scale

See Section 9.4.

Abbreviations: RCT, randomised controlled trial.

The results of the study by Han *et al.* (2002) are shown in Table 204. Soy had a beneficial effect upon all sub-categories of the Kupperman Index (including vasomotor symptoms and insomnia) when compared to placebo. The results suggest that isoflavones are efficacious at relieving menopausal symptoms. This result is in contrast to the studies included in the Kronenberg *et al.* (2002) systematic review where none of the five included studies demonstrated a significant benefit. Furthermore, as the study by Han *et al.* (2002) had less than 50 subjects in each arm, it should not be given undue consideration.

TABLE 204 CAM: GLOBAL MENOPAUSAL SYMPTOM AND QOL SCALES — ORIGINAL STUDY RESULTS (KUPPERMAN INDEX; HAN *ET AL.*, 2002)

Symptom	Time of measurement	Isoflavone Mean (SEM)	Placebo Mean (SEM)	P value
TOTAL	Baseline	44.6 (1)	40.3 (1.2)	< 0.01
	Endpoint	24.9 (1.7)	41.6 (1.1)	

Abbreviations: SEM, standard error of the mean.

The results of the study examining the efficacy of black cohosh by Wuttke *et al.* (2003) are summarised in Table 205. The results show that there is no statistically significant difference in the change from baseline of the MRS score for black cohosh compared with placebo. In addition, a large placebo effect is seen.

TABLE 205 CAM: GLOBAL MENOPAUSE SYMPTOM AND QOL SCALES — ORIGINAL STUDY RESULTS (MRS; WUTTKE *ET AL.*, 2003)

Symptom	Treatment	Decrease in MRS total score <sup>a</sup>	P value <sup>b</sup>
MRS	Black cohosh	1.8	0.051
	Placebo	1.5	-
	Conjugated oestrogens	1.8	0.051

Abbreviations: MRS, Menopause Rating Scale.

<sup>a</sup> Estimated from graph

<sup>b</sup> Comparison with placebo