### Key question: (CAM1) Do complementary therapies, when compared to conventional treatments, delay disease progression and mortality in men with advanced prostate cancer?

(Circle appropriate grade for each component)

<table>
<thead>
<tr>
<th>Evidence table ref: Table 3- 6</th>
</tr>
</thead>
</table>

### 1. Volume of evidence (quantity level, methodological quality and relevance to patients of the body of evidence for this question, based on critical appraisal of each individual study according to Minimum Requirements)

| | Evidence table ref: Table 3- 6 |
|--------------------------------|

Seven low quality RCTS dealing with 7 different dietary supplements (Vitamin D (calcitriol), Folinic acid, Ellagic acid, Lycopene, PC-SPES, Verum, Soy-based); only one of which (Beer 2006/Reddy 2005) included more than 100 patients. There were 4 trials for men with hormone refractory disease, one placebo controlled (Beer 2006/Reddy 2005), one trial for men with metastases who had just undergone surgical castration (Ansari 2003) and 2 placebo controlled trials for men with rising PSA levels following definitive therapy (Schroder 2005, Kranse 2005); only the latter 2 trials were placebo controlled however these only examined effects on PSA levels.

For hormone refractory disease three of the trials examined the effects of adding a dietary supplement to chemotherapy and the fourth compared a nutritional supplement with oestrogen therapy. **C**

<table>
<thead>
<tr>
<th>Grade</th>
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</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

### 2. Consistency (the degree of consistency demonstrated by the available evidence. Where there are conflicting results indicate how the group forms a judgement as to the overall direction of the evidence)

**Each trial examined a different intervention.**

Four trials reported survival outcomes; for hormone refractory disease high doses (45 ug) of calcitriol weekly significantly increased median survival for patients receiving docetaxel chemotherapy from 16 months in the control arm to 23 months; no significant survival benefit was seen with the addition of folic acid to fluorouracil chemotherapy or ellagic acid to vinorelbine/estramustine chemotherapy. For men with metastases who had undergone an orchiectomy lycopene significantly decreased mortality from 44% to 26% and significantly reduced progression. For men with rising PSA a mixture of plant extracts, vitamins and minerals significantly slowed the rise in total PSA in the per protocol but not intention to treat analyses (Schroder) and a second mixture of dietary extracts significantly reduced free PSA doubling times (Kranse). Neither study reported clinical outcomes and the possibility that a component may have masked PSA levels cannot be discounted. **C**

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### 3. Clinical impact
(The potential impact of recommendation i.e. size of patient population, relevance of outcomes to the question, balance of risks and benefits, relative benefit over other management options, resource and organisational implications)

For men with metastases being treated with orchiectomy the addition of lycopene increased median survival by 4 months from 9 to 13 months and was associated with an absolute difference in survival of 18% with a mean follow-up 25.5 months i.e for every 5 men treated with lycopene one would experience a survival benefit. Median survival rates suggest that a significant proportion of men may have had hormone resistant disease. For men with HRPC receiving docetaxel chemotherapy median overall survival increased by 7 months with the addition of calcitriol. For toxicity results see the template for CAM question 3.

<table>
<thead>
<tr>
<th>Recommendation</th>
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</tr>
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<tbody>
<tr>
<td>Excellent (very large clinical impact)</td>
<td>A</td>
</tr>
<tr>
<td>Substantial clinical impact</td>
<td>B</td>
</tr>
<tr>
<td>Moderate clinical impact</td>
<td>C</td>
</tr>
<tr>
<td>Slight or restricted clinical impact</td>
<td>D</td>
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</tbody>
</table>

### 4. Generalisability
(How reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline?)

The lycopene study was carried out in India. Potentially different diet and treatment options may limit the generalisability of this study – note median survival for men with bone metastases was 9 and 13 months post orchietomy. Men who had undergone previous radiotherapy, hormone therapy or chemotherapy were excluded. The daily dose of 4mg/day is slightly higher than the average daily intake of 3.7mg for a group of Australian men aged 55 years or older. Only one of the chemotherapy treatments used in conjunction with dietary supplements, docetaxel, is regularly used in current practice so the results from the Vitamin D study are generalisable (Beer2006/Reddy 2005).

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<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>Directly generalisable to target population with some caveats</td>
<td>B</td>
</tr>
<tr>
<td>Probably applicable to Australian healthcare context with some caveats</td>
<td>C</td>
</tr>
<tr>
<td>Not directly generalisable to target population and hard to judge whether it is sensible to apply</td>
<td>D</td>
</tr>
</tbody>
</table>

### 5. Applicability
(The extent to which the body of evidence is directly applicable to Australian healthcare context)

Only lycopene and folinic acid are available in Australia. The results for lycopene may apply to only a small group of men in Australia as the use of LHRH agonists has replaced surgical castration (orchiectomy) and frequently introduced before evidence of metastases.

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<tr>
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</tbody>
</table>

**Other factors**

Indicate here any factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)
The calcitriol trial ASCENT I of 250 men was followed by a larger trial of the same intervention in 2006 with a planned accrual of 1200 men. This trial was terminated in November 2007 when the Data Safety Monitoring Board observed a higher death rate in the calcitriol arm.

### EVIDENCE STATEMENT
Please summarise the development group’s synthesis of the evidence relating to the key question, taking all of the above factors into account. Please indicate any dissenting opinions.

There were 7 RCTs examining 7 different treatments.

For men with hormone resistant disease a trial of 250 men produced weak evidence that high doses of calcitriol as an adjuvant to docetaxel chemotherapy could improve survival. However in a recent larger trial of the same intervention (ASCENT II) a higher death rate was observed with calcitriol resulting in the termination of the trial.

For men with metastatic disease starting hormone deprivation in the 2 years following orchietomy, lycopene resulted in 18% absolute increase in survival.

Nutritional and herbal supplements may slow PSA increase. However until there is evidence of improved clinical outcomes this should be treated with caution as PSA levels can be masked by certain drugs.

### RECOMMENDATION
What recommendation(s) does the guideline development group draw from this evidence?

Calcitriol **not** to be used in HRPC due to excess deaths in one study.

**Grade A**

Lycopene may benefit a small group of men who have metastatic prostate cancer who have had no radiotherapy, no hormone therapy and who have had orchidectomy.

**Grade C**

There is insufficient evidence to recommend any other complementary therapies.

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<td>C</td>
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<tr>
<td>Clinical impact</td>
<td>Satisfactory</td>
<td>C</td>
</tr>
<tr>
<td>Generalisability</td>
<td>Satisfactory</td>
<td>C</td>
</tr>
<tr>
<td>Applicability</td>
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<td>C</td>
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</table>

The overall grade is the summation of the grades for individual components. A recommendation cannot be graded A or B unless the volume and consistency of evidence are both either A or B.

**GRADE OF RECOMMENDATION**

A/C
### Key question: (CAM2) Do complementary therapies, when compared to conventional treatments, provide pain relief and improve the quality of life of men with advanced prostate cancer?

(Circle appropriate grade for each component)

<table>
<thead>
<tr>
<th>Evidence table ref: Table 7, 8</th>
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</table>

### 1. Volume of evidence (quantity level, methodological quality and relevance to patients of the body of evidence for this question, based on critical appraisal of each individual study according to Minimum Requirements)

3 small low quality RCTs examined the effects of CAM on pain or QOL. For men with hormone resistant prostate cancer one study examined the effects of folinic acid as an adjuvant to fluorouracil chemotherapy on pain and one study examined the effects of ellagic acid as an adjuvant to Vinorelbine/estramustine chemotherapy on pain and performance status. The third study examined the effect of lycopene in addition to orchiectomy on analgesia for men with metastatic disease (89 – 93% had painful bone metastases).

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### 2. Consistency (the degree of consistency demonstrated by the available evidence. Where there are conflicting results indicate how the group forms a judgement as to the overall direction of the evidence)

Each study examined a different treatment. It was not possible to determine whether or not adjuvant folinic acid or adjuvant lycopene improved pain levels. Ellagic acid significantly reduced analgesic use but not actual pain relief or performance status.

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### 3. Clinical impact (the potential impact of recommendation i.e. size of patient population, relevance of outcomes to the question, balance of risks and benefits, relative benefit over other management options, resource and organisational implications)

Very little evidence of any benefit.

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### 4. Generalisability (how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline?)

No evidence for the use of CAM therapies with hormone and chemotherapies currently used in clinical practice.

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</table>
5. Applicability *(the extent to which the body of evidence is directly applicable to Australian healthcare context)*

Ellagic acid is not available in Australia and comparisons are not applicable to Australian practice.

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**Other factors**

*Indicate here any factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

**EVIDENCE STATEMENT**

*Please summarise the development group’s synthesis of the evidence relating to the key question, taking all of the above factors into account. Please indicate any dissenting opinions*

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**RECOMMENDATION**

*What recommendation(s) does the guideline development group draw from this evidence?*

There is insufficient evidence to make any recommendations on dietary supplements in relation to quality of life and pain relief.

**GRADE OF RECOMMENDATION**

C
Key question: (CAM3) What is the toxicity of complementary therapies used in the management of advanced prostate cancer?

<table>
<thead>
<tr>
<th>Evidence table ref: Table 9, 10</th>
</tr>
</thead>
</table>

1. **Volume of evidence** *(quantity level, methodological quality and relevance to patients of the body of evidence for this question, based on critical appraisal of each individual study according to Minimum Requirements)*

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There was no toxicity data reported for lycopene or the herbal supplements.

Four of the seven low quality RCTs examined toxicity and the largest trial studied 250 men.

Three trials of adjuvant CAM with chemotherapy examined haematological toxicities, gastrointestinal toxicities and other different adverse events. Two trials (Beer 2006/Reddy 2005; Bruel 1997) examined differences in all serious toxicities/adverse events. The fourth trial compared PC-SPES with diethylstilbestrol and examined gastrointestinal toxicities and a range of adverse events.

2. **Consistency** *(the degree of consistency demonstrated by the available evidence. Where there are conflicting results indicate how the group forms a judgement as to the overall direction of the evidence)*

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Weekly high dose calcitriol as an adjuvant to docetaxel did not significantly reduce serious toxicities other than thrombosis. There was no evidence of significant harm with no serious calcemic adverse events reported in either arm (125 men per arm) However the number of grade I-II calcemic events if any was not reported and it is unclear as to how frequently calcium levels were monitored.

Folinic acid as an adjuvant to fluorouracil chemotherapy significantly reduced the incidence of leucopenia and did not significantly increase the rate of more serious toxicities.

Ellagic acid as an adjuvant to vinorelbine/estramustine chemotherapy significantly reduced the incidence of neutropenia, anaemia and anorexia but did not significantly reduce gastrointestinal toxicities. There was no evidence as to whether ellagic acid affected rates of all serious adverse.

PS-SPES and Diethylstilbestrol did not differ significantly for a number of different toxicities.

3. **Clinical impact** *(the potential impact of recommendation i.e. size of patient population, relevance of outcomes to the question, balance of risks and benefits, relative benefit over other management options, resource and organisational implications)*
The benefits of folinic acid and ellagic acid were seen in patients treated with chemotherapy regimens no longer routinely used.

Calcitriol can cause hypercalcemia at daily doses of slightly higher than standard replacement doses. In a group of 125 men a weekly high dose of calcitriol as an adjuvant to docetaxel chemotherapy did not appear to be associated with serious toxicities. Given the absence of information on how the men were monitored and the incidence of lower grade hypercalcemia there are significant reservations about the safety of this treatment. There was no evidence regarding the toxicity of lycopene.

4. Generalisability (how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline?)

<table>
<thead>
<tr>
<th>Factor</th>
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</thead>
<tbody>
<tr>
<td>Folinic acid and ellagic acid were not used with current standard chemotherapy. High dose calcitriol was examined as an adjuvant to currently used chemotherapy (docetaxyl). PC –SPES is not available in Australia and was found to contain a number of drugs including synthetic oestrogens.</td>
<td>A: Excellent (directly generalisable to the target population)</td>
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<tr>
<td>B: Good (directly generalisable to target population with some caveats)</td>
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</tr>
<tr>
<td>C: Satisfactory (not directly generalisable to the target population but could be sensibly applied to patients of interest, little to generalise but reasonable)</td>
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<tr>
<td>D: Poor (not directly generalisable to target population and hard to judge whether it is sensible to apply) nil to apply</td>
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5. Applicability (the extent to which the body of evidence is directly applicable to Australian healthcare context)

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<tr>
<td>Folinic acid and lycopene are available in Australia. Ellagic acid, PC-SPES and high dose calcitriol are not available in Australia. High dose calcitriol toxicity has not been fully explored and as such any application would require careful monitoring and control.</td>
<td>A: Excellent (directly applicable to Australian healthcare context)</td>
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<td>B: Good (applicable to Australian healthcare context with few caveats)</td>
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Other factors

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The calcitriol trial ASCENT I of 250 men was followed by a larger trial of the same intervention in 2006 with a planned accrual of 1200 men. This trial was terminated in November 2007 when the Data Safety Monitoring Board observed a higher death rate in the calcitriol arm.

EVIDENCE STATEMENT

Please summarise the development group’s synthesis of the evidence relating to the key question, taking all of the above factors into account. Please indicate any dissenting opinions
There is a paucity of information on the toxicity of dietary supplements in advanced prostate cancer.

In a randomised phase II study of 250 men weekly high doses of calcitriol appeared not to be toxic however all grades of hypercalcaemia were not reported in this study. Increased mortality with the addition of calcitriol has since been observed in a larger study.

The toxicity of lycopene is unknown. No evidence was found regarding the beneficial or harmful effects of lycopene on toxicity.

Folinic acid and ellagic acid may reduce some toxic effects of chemotherapy however the benefits were seen for chemotherapies no longer regularly used for prostate cancer.

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**RECOMMENDATION**

*What recommendation(s) does the guideline development group draw from this evidence?*

Calcitriol **not** to be used in HRPC due to excess deaths in one study.

Grade A

There is insufficient evidence to make any recommendations on dietary supplements in relation to toxicity.

Grade C

The overall grade is the summation of the grades for individual components. A recommendation cannot be graded A or B unless the volume and consistency of evidence are both either A or B.

**GRADE OF RECOMMENDATION**

A/C