### Hormone therapy question 12: What is the incidence of osteoporosis and reduction in bone mineral density at 2, 5 and 10 years and what is the risk of osteoporotic bone fracture due to bilateral orchidectomy (or orchidectomy), LHRH agonist or long term androgen deficiency? (Circle appropriate grade for each component)

### Evidence ref: Tables 5-10 in hormone therapy question 12 report

#### 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)

| Although there is a considerable volume of publications, the manuscripts are of lower-level evidence with the exception of two randomised studies (Smith et al, 2004; Sieber et al, 2004) comparing bone mineral densities (BMD) in patients randomised to bicalutamide or LHRH agonists. Other studies reporting BMD and fracture rates with androgen deprivation therapy (ADT) in both non-localised and metastatic prostate cancer were observational with results from both prospective and retrospective analyses of hospital and collated organisational data. Many studies had industry support including the two randomised studies (above) which were supported by AstraZeneca; the second of these recruited twice the number of patients required for the difference stated in their power calculations. | A Excellent (several level I or II studies with low risk of bias)  
B Good (one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias)  
C Satisfactory (Level III studies with low risk of bias or Level I or II studies with moderate risk of bias)  
D Poor (Level IV studies or Level I to III studies with high risk of bias) |

#### 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)

| From the variety of study designs, the results were consistent in terms of BMD being reduced with LHRH agonists and bilateral orchidectomy, increasingly so over time, but maintained (or slightly increased) with bicalutamide monotherapy. There was an increased likelihood of fractures over time with LHRH agonist therapy and bilateral orchidectomy although likelihood estimates varied, reflecting differences in study designs and criteria. The data needs to also be considered in light of the known data regarding bone biology and how testosterone depletion (and its consequent decrease in oestrogen) does cause bone mineral depletion. In other words the data is consistent with the known biology. | A Excellent (all studies consistent)  
B Good (most studies consistent and inconsistency can be explained)  
C Satisfactory (some inconsistency, reflecting genuine uncertainty around question)  
D Poor (evidence is inconsistent) |

#### 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 significant clinical impact of BMD changes is based on reports of a not inconceivable background of osteopaenia in patients at baseline and the reasonable presumption that continuing reductions in BMD predispose to clinically meaningful outcomes of osteoporosis and associated fractures. It is also worth noting that the clinical significance of osteoporotic fracture is greater for hip rather than vertebral bodies because of the related high mortality rate with the former. | A Excellent (very large clinical impact)  
B Good (substantial clinical impact)  
C Satisfactory (moderate clinical impact)  
D Poor (slight or restricted clinical impact) |
4. **Generalisability** *(how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline?)*

| A | Excellent (directly generalisable to the target population) |
| B | Good (directly generalisable to target population with some caveats) |
| C | Satisfactory (not directly generalisable to the target population but could be sensibly applied) |
| D | Poor (not directly generalisable to target population and hard to judge whether it is sensible to apply) |

Although a number of factors are operative in reducing BMD, LHRH agonist therapy and bilateral orchidectomy both directly and indirectly reduce BMD with this tendency continuing over time thus increasing the likelihood of pathological fractures from osteoporosis.

Bicalutamide monotherapy does not result in reductions in BMD. Oestrogen monotherapy may also preserve BMD (Eriksson, 1995).

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

| A | Excellent (directly applicable to Australian healthcare context) |
| B | Good (applicable to Australian healthcare context with few caveats) |
| C | Satisfactory (probably applicable to Australian healthcare context with some caveats) |
| D | Poor (not applicable to Australian healthcare context) |

The findings are directly applicable to the Australian population to the extent that LHRH agonists and, to a lesser extent, bilateral orchidectomy are the only primary forms of androgen therapy either as monotherapy or part of CAB.

The evidence provided in favour of bicalutamide monotherapy having a BMD-protective property is not relevant as this agent (and class of drug) is not approved for use as monotherapy in Australia. There is insufficient evidence to make a definite comment on intermittent androgen deprivation although temporary stabilisation of bone loss may result from temporary cessation (Higano, 2004). Similarly, information is insufficient to make a comment with respect to whether there is a worse or diminished effect on BMD with combined androgen blockade (CAB) versus castration monotherapy. The approved combinations for CAB by the Pharmaceutical Benefits Scheme in Australia are LHRH agonist and bicalutamide/flutamide or bilateral orchidectomy plus nilutamide.

**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 methods used to measure BMD changes were inconsistent as there were a variety of measures (with varying degrees of surrogacy for development of osteoporosis) used. The dual energy x-ray absorptiometry (DEXA) was the most commonly employed measurement used to target the most clinically-relevant sites of hips and vertebral bodies. There were fewer manuscripts reporting use of the more sensitive barometer of quantitative computerised tomography but which exposes patients to more radiation and is subject to quality control issues.

The criteria used for reporting changes in BMD varied reflecting a lack of accepted and standardised/validated yardsticks for men compared with those agreed and accepted for women.

A not inconsiderable proportion of men proceeding to ADT are osteopaenic at baseline and this needs to be considered when interpreting the data.
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

For men with prostate cancer, both LHRH agonists and bilateral orchidectomy significantly reduce BMD, continuing to do so over time, resulting in an increased likelihood of pathological fracture of vertebral bodies and hips from osteoporosis. The clinical significance of this is more relevant for men destined to live for many years (ie rising PSA with no radiographic evidence of disease, ADT as primary therapy for organ confined disease or in the adjuvant setting) and less relevant for men starting ADT for metastatic disease. There is insufficient evidence to make a definite comment on intermittent androgen deprivation. There is insufficient evidence to make a comment with respect to whether there is a worse or diminished effect on BMD with combined androgen blockade (CAB) versus castration monotherapy. Bicalutamide monotherapy is not associated with reductions in BMD.

Component | Descriptor | Grade
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Volume of evidence | Satisfactory | C
Consistency | Good | B
Clinical impact | Good | B
Generalisability | Excellent | A
Applicability | Satisfactory | C

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

Before commencing patients on ADT consider the likely duration of that treatment, the risk benefit analysis for the indication for treatment and take into account the effects on BMD and risks of pathological fractures from osteoporosis. In addition, consider BMD measurements at baseline and subsequently during treatment with the possibility of instituting preventative measures (calcium, vitamin D and exercise) as is appropriate for good bone health and use of bisphosphonates as indicated by PBS for osteoporosis.

GRADE OF RECOMMENDATION | C
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