

## 5.23 RADIUM (223Ra)

### radium (223Ra) dichloride 6.6 MBq/6mL injection, 6mL, Xofigo<sup>®</sup>, Bayer Australia Ltd

#### 1 Purpose of application

- 1.1 To request an Authority Required Section 100 listing for radium (223Ra) for treatment of castration resistant metastatic carcinoma of the prostate.
- 1.2 The requested basis for listing was a cost-minimisation analysis of 223Ra and abiraterone.

#### 2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

##### Essential elements of the requested listing

| Name, restriction, manner of administration, form         | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Ex-manufacturer price*                          | Proprietary name and manufacturer |
|---|--------------------------|--------------------------|----------------|---|-----------------------------------|
| RADIUM-223, 6mL/20 mL vial (6 MBq)a for IV administration | 1                        | 1                        | 5              | \$7022.79 (public)<br>\$ [REDACTED] (effective) | XOFIGO, Bayer Australia Ltd       |

\*The listing of 223Ra on the PBS will require a new Section 100 program for radiopharmaceuticals to be developed. This arrangement would, amongst other things, set out any mark-ups and fees associated with the delivery of radiopharmaceuticals through the PBS. In the absence of a section 100 arrangement, the prices reported above are the proposed ex-manufacturer prices.

The submission requests a special pricing arrangement.

|                         |   |
|-------------------------|---|
| <b>Category/Program</b> | Section 100 – new program (name to be confirmed)  |
| <b>PBS Indication:</b>  | Castration resistant metastatic carcinoma of the prostate   |
| <b>Restriction:</b>     | <input checked="" type="checkbox"/> Authority Required - In Writing<br><input checked="" type="checkbox"/> Authority Required – Telephone |

|                                |  |
|--------------------------------|--|
| <b>Clinical criteria:</b>      | <p>Patients must have <math>\geq 2</math> skeletal metastases<br/> AND<br/> Patient must have a WHO performance status of 2 or less<br/> AND<br/> Patient must have failed treatment with docetaxel due to resistance or intolerance; OR<br/> Patient must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel<br/> AND<br/> The treatment must not be used in combination with chemotherapy.<br/> AND<br/> <i>The patient must not receive PBS-subsidised 223Ra if progressive disease develops while on 223Ra</i><br/> AND<br/> <i>The patient must not have received prior treatment with abiraterone or enzalutamide; OR</i><br/> <i>The patient must have developed intolerance to enzalutamide requiring permanent withdrawal</i><br/> AND<br/> <i>The patient must have developed intolerance to abiraterone requiring permanent withdrawal.</i></p> |
| <b>Prescriber Instructions</b> | <p>A maximum of six (6) intravenous injections are to be administered at four-weekly intervals.</p>  |
| <b>Administrative Advice</b>   | <p>Special Pricing Arrangements apply.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>At the pre-calibrated reference date of 14 days, the radioactive concentration is 1000 kilobecquerels (kBq)/mL. If administered on a day other than the reference date, the volume is adjusted according to the physical decay table supplied with each shipment.</p>   |

*For more detail on PBAC’s view, see section 6 PBAC Outcome.*

### 3 Background

- 3.1 223Ra was registered by the TGA on 20 May 2014 for use in Australia for the treatment of castration-resistant prostate cancer patients with symptomatic bone metastases and no known visceral metastatic disease.
- 3.2 At its meeting of 3 – 4 April 2014, the Medical Services Advisory Committee (MSAC) recommended 223Ra for the treatment of patients with symptomatic castrate resistant prostate cancer with skeletal metastases (Application No. 1268). This recommendation was made on the basis of mixed cost-utility analyses against best supportive care (BSC), strontium-89 and samarium-153 lexidronam and cost-minimisation analyses against cabazitaxel and abiraterone.
- 3.3 The administration of strontium-89 was first listed on the MBS in 1997. The administration of samarium-153 lexidronam was listed on the MBS in 2000.
- 3.4 Although noting that the evidence base was not strong, the MSAC accepted the following conclusions with respect to the comparative effectiveness and safety of 223Ra and its comparators.

**Table 1: MSAC therapeutic conclusions for 223Ra versus the relevant comparators**

| Comparator              | Overall survival | Time to first SRE   | Bone pain           | Quality of life | Adverse events                      |
|-------------------------|------------------|---------------------|---------------------|-----------------|-------------------------------------|
| Abiraterone             | Non-inferior     | Non-inferior        | Non-inferior        | Non-inferior    | Non-inferior                        |
| Enzalutamide*           | Non-inferior     | Non-inferior        | Non-inferior        | Non-inferior    | Non-inferior                        |
| Cabazitaxel             | Non-inferior     | Non-inferior        | Non-inferior        | Non-inferior    | <del>Non-inferior</del><br>Superior |
| Strontium-89            | Superior         | Assume non-inferior | Assume non-inferior | Non-inferior    | Non-inferior                        |
| Samarium-153 lexidronam | Superior         | Assume non-inferior | Assume non-inferior | Non-inferior    | Non-inferior                        |
| BSC                     | Superior         | Superior            | Superior            | Superior        | Non-inferior                        |

BSC = best supportive care; SRE = skeletal-related event

\*Added enzalutamide as it has been PBS listed since 2014, and was recommended on the basis of a cost minimisation with abiraterone.

3.5 This was the first application to the PBAC for 223Ra. This earlier MSAC recommendation has not been given effect, as the MBS is not able to accommodate the requested Special Pricing Arrangement.

## 4 Comparator

4.1 The submission nominated abiraterone as the comparator. In nominating abiraterone as the comparator, the submission implicitly nominates cabazitaxel as a partial comparator and enzalutamide as a full alternative comparator:

- Cabazitaxel is implicitly a comparator for 50% of patients as abiraterone was recommended for listing on a cost-minimisation basis against cabazitaxel (50%), and a cost-effectiveness basis against BSC.
- Enzalutamide is implicitly a comparator as it was recommended on a cost-minimisation basis with abiraterone.

4.2 The submission acknowledges that the MSAC considered a mixed comparator approach against BSC, strontium-89 and samarium-153 lexidronam, cabazitaxel and abiraterone, to be appropriate. The submission argued that 223Ra has been accepted by MSAC to be superior in terms of effectiveness to best supportive care, strontium-89 and samarium-153 lexidronam.

4.3 The submission argued that non-withstanding the MSAC conclusion that 223Ra was non-inferior in terms of effectiveness and safety to cabazitaxel, the available evidence supported a conclusion of superior safety for 223Ra over cabazitaxel.

4.4 The submission also argued that there is an unmet clinical need for treatments post-progression with abiraterone or enzalutamide, and that 223Ra will be used in this setting. The MSAC considered that some 223Ra use would be as an alternative to other PBS listed treatments, and some use would be sequential. The PBAC may wish to consider whether BSC is the more appropriate comparator for sequential use, or alternatively, if the restriction for 223Ra should be amended to allow patients to receive one of abiraterone, enzalutamide or 223Ra.

*For more detail on PBAC's view, see section 6 PBAC Outcome.*

## 5 Consideration of the evidence

### *Sponsor hearing*

5.1 There was no hearing for this item as it was a minor submission.

### *Consumer comments*

5.2 There PBAC noted and welcomed the input from individuals (9), health care professionals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with 223Ra including the improvement of quality of life (QOL), increased mobility, reduced pain, fewer side effects and a reduction in hospital visits. The organisation submissions from the Prostate Cancer Foundation of Australia and the Prostate Heidelberg Cancer Supporters Group, highlighted the above benefits and urged access to the already MSAC approved treatment for Australians as a matter of urgency and highlight the inequity of access to this treatment that is available internationally.

5.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the 223Ra submission, on the basis of improved PFS, OS and improved QOL. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for 223Ra, which was 5 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>1</sup>, based on a comparison with abiraterone and cabazitaxel.

### *Clinical trials*

5.4 The submission does not present any clinical evidence that was not included in the MSAC submission.

5.5 The MSAC evaluation of comparative safety and effectiveness against cabazitaxel and abiraterone was based on:

- an indirect comparison of 223Ra and cabazitaxel based on the ALSYMPCA trial of 223Ra and one randomised comparative trial comparing cabazitaxel and placebo (TROPIC); and
- an indirect comparison of 223Ra and abiraterone based on the ALSYMPCA trial of 223Ra and one randomised comparative trial comparing abiraterone and placebo (COU-AA-301) (MSAC PSD for 223Ra, April 2014)

The same abiraterone and cabazitaxel clinical trials were considered by the PBAC for the application to list abiraterone.

### *Comparative effectiveness*

5.6 The MSAC considered that 223Ra is probably non-inferior to cabazitaxel and abiraterone in terms of overall survival (indirect HR 0.99; 95% CI: 0.78, 1.27 for

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<sup>1</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

cabazitaxel and indirect HR 0.94; 95% CI: 0.74, 1.19 for abiraterone), time to first skeletal-related event (indirect HR 0.99; 95% CI: 0.68, 1.45 for abiraterone) and improvement in bone pain (indirect OR 0.61; 95% CI: 0.30, 1.24 for cabazitaxel and indirect OR 0.69; 95% CI: 0.47, 1.01 for abiraterone). The MSAC noted that its conclusions of non-inferiority involving abiraterone and cabazitaxel were supported by the evidence in the presented indirect comparisons. (MSAC PSD for 223Ra, April 2014)

### ***Comparative harms***

- 5.7 The MSAC concluded that the indirect comparisons showed that 223Ra is probably non-inferior to cabazitaxel and abiraterone in terms of safety. However, MSAC noted that the indirect comparisons had low power for assessing adverse events.
- 5.8 The submission claims that 223Ra has safety advantages over cabazitaxel that are similar to the safety advantages accepted by the PBAC for abiraterone over cabazitaxel.
- 5.9 Specifically, the submission provides a summary of the Grade  $\geq$  3 haematological adverse events across the ALSYMPCA, 301 and TROPIC trials (reproduced at Table 2). Haematological adverse events in cabazitaxel were higher compared to 223Ra and abiraterone.
- 5.10 The results of an indirect comparison for neutropenia ( $\geq$  Grade 3) and febrile neutropenia for 223Ra, abiraterone and cabazitaxel conducted by the submission are reproduced in Table 3 and Figure 1. The rate of neutropenia was statistically significantly lower for 223Ra compared to cabazitaxel (RD= -0.222, CI 95% -0.288, -0.157, p=0.000) with a NNT of 5 patients. Furthermore, the rate of febrile neutropenia was statistically significantly lower for 223Ra compared to cabazitaxel (RD= -0.064, CI 95% -0.094, -0.033, p=0.000) with a NNT of 16 patients. The submission concludes that the safety analysis demonstrates that the safety profile is similar between 223Ra and abiraterone.

**Table 2: Summary of adverse events (≥ Grade 3)**

|                       | ALSYMPCA                   |                 | COU-AA-301                          |                                 | TROPIC                              |                                      |
|-----------------------|----------------------------|-----------------|-------------------------------------|---------------------------------|-------------------------------------|--------------------------------------|
|                       | Radium-223 (N=600)         | Placebo (N=301) | Abiraterone plus prednisone (N=791) | Placebo plus prednisone (N=394) | Cabazitaxel plus prednisone (N=371) | Mitoxantrone plus prednisone (N=371) |
| <b>Haematological</b> |                            |                 |                                     |                                 |                                     |                                      |
| Anaemia               | 76 (13)                    | 40 (13)         | 62 (8)                              | 32 (8)                          | 39 (11)                             | 18 (5)                               |
| Thrombocytopenia      | 39 (7)                     | 6 (2)           | 11 (1)                              | 2 (1)                           | 15 (4)                              | 6 (2)                                |
| Neutropenia           | 13 (2)                     | 2 (1)           | 1 (<1)                              | 1 (<1)                          | 303 (82)                            | 215 (58)                             |
| Febrile neutropenia   | 1 (<1)                     | 1 (<1)          | 3 (<1)                              | 0 (0)                           | 28 (8)                              | 5 (1)                                |
| Leukopenia            | -                          | -               | -                                   | -                               | 253 (68)                            | 157 (42)                             |
| Source:               | Parker et al 2013; Table 3 |                 | Fizazi et al 2012; Table 5          |                                 | DeBono et al 2010; Table 4          |                                      |

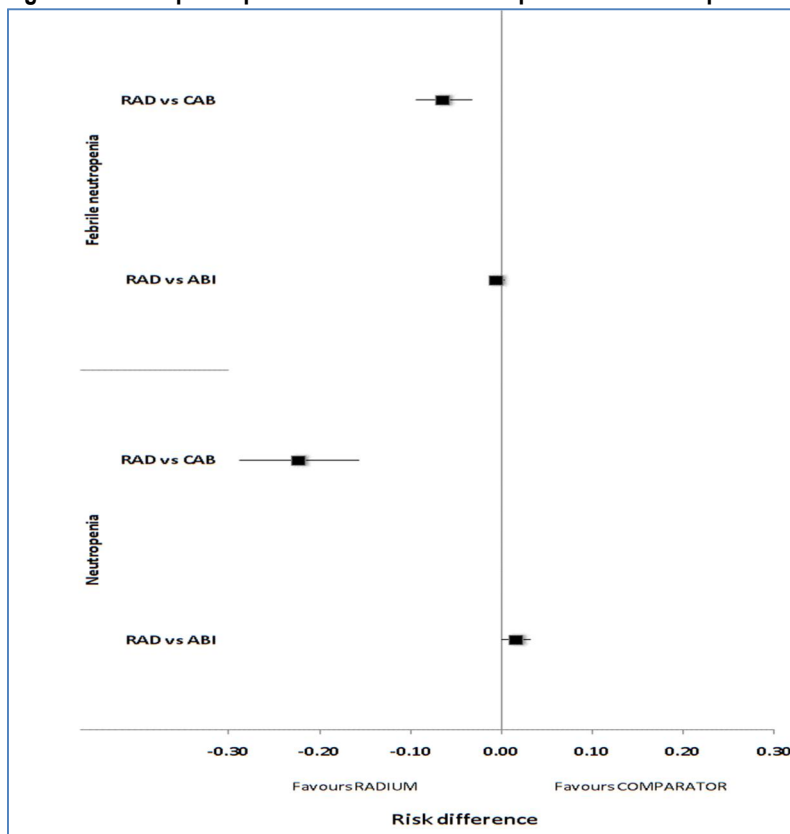
Source: submission Table 13, pp 50

**Table 3: Indirect comparisons (Grade ≥3 adverse events)**

|                            | Proportion of subjects<br>RD [95% CI]<br>Result <0 favours active treatment |                                      |  | Indirect RD [95% CI]; p-value<br>Result <0 favours Radium-223 |   |
|----------------------------|---|--------------------------------------|--|---|---|
|                            | Radium-223 vs. PBO (ALSYMPCA)   | Abiraterone vs. PBO (COU-AA-301)     | Cabazitaxel vs. PBO (TROPIC)                     | Radium-223 vs. Abiraterone                                    | Radium-223 vs. Cabazitaxel                                |
| <b>Neutropenia</b>         | 0.02 vs.0.01<br>0.02 [0.00, 0.03]   | 0.01 vs. 0.01<br>-0.00 [-0.01, 0.00] | <b>0.82 vs. 0.58</b><br><b>0.24 [0.17, 0.30]</b> | 0.016<br>[0.000, 0.032];<br>0.044                             | <b>-0.222</b><br><b>[-0.288, -0.157];</b><br><b>0.000</b> |
| <b>Febrile neutropenia</b> | 0.00<br>[-0.01, 0.01]   | 0.00<br>[0.00, 0.01]                 | <b>0.06</b><br><b>[0.03, 0.09]</b>               | -0.005<br>[-0.014, 0.003];<br>0.206                           | <b>-0.064</b><br><b>[-0.094, -0.033];</b><br><b>0.000</b> |

Source: submission Table 14, pp 51

Figure 1: Forest plot representation: Indirect comparison for neutropenia and febrile neutropenia



Source: PBAC submission, Figure 14.

5.11 The MSAC concluded that the indirect comparisons had lower power to enable conclusions to be drawn about safety. However the PBAC has previously acknowledged that abiraterone has a safety advantage over cabazitaxel.

### ***Interpretation of clinical evidence***

5.12 The submission claimed that:

- 223Ra is non-inferior versus abiraterone in terms of safety and effectiveness

5.13 Thus indirectly:

- 223Ra is non-inferior versus enzalutamide in terms of safety and effectiveness; and
- 223Ra is superior versus cabazitaxel in terms of safety and non-inferior in terms of effectiveness.

5.14 The PBAC considered that the claim of non-inferior comparative effectiveness against abiraterone, enzalutamide and cabazitaxel was reasonable.

5.15 The PBAC considered that the claim of non-inferior safety against abiraterone and enzalutamide and superior comparative safety against cabazitaxel was reasonable.

### ***Economic analysis***

5.16 The submission presented a cost minimisation analysis against abiraterone. The PBAC agreed this was a reasonable approach.

5.17 The equi-effective doses for the purposes of the cost-minimisation analysis against abiraterone are considered by the submission to be

5.1 x 223Ra cycles = 1g abiraterone daily for 8 x 30 day cycles (240 days).

5.18 5.1 was the average number of radium injections per patient observed in the ALSYMPCA trial.

5.19 The submission claimed that the average number of cycles of abiraterone per patient in the CU301 trial was 8. The PBAC recalled that the public summary document (PSD) for abiraterone reported that the median number of cycles of abiraterone used in the CU 301 clinical trial was 7.5 rather than the 8 as claimed by the submission (abiraterone PSD July 2012). The PBAC agreed it was appropriate to use 5.1 cycles of 223Ra in the cost-minimisation analysis.

5.20 The submission’s cost-minimisation analysis is included at Table 4. This analysis includes offsets for the cost of administration (223Ra), concomitant corticosteroids (abiraterone) and concomitant liver function tests (abiraterone).

**Table 4: Submission’s cost-minimisation analysis of 223Ra vs abiraterone**

| <b>Cost of abiraterone treatment, full course of treatment</b> |             |                |                  |                  |
|--|-------------|----------------|------------------|------------------|
| Resource use   | Unit cost   | Unit per cycle | Treatment cycles | Total per course |
| Abiraterone drug acquisition                                   | \$3,603.06* | ■              |                  | ■■■■■<br>■■■■■   |
| Co-med drug acquisition, 5 mg prednisolone                     | \$14.09     | ■              | ■■■              | ■■■■■<br>■■■■■   |
| Liver function test  | \$■■■       | ■■■            |                  | ■■■■■<br>■■■■■   |
| Total, abiraterone for full course of treatment                |             |                |                  | ■■■■■<br>■■■■■   |
| <b>Cost-minimising pricing of 223Ra</b>                        |             |                |                  |                  |
| Equi-potent dose / cycle numbers of 223Ra vs abiraterone       |             |                |                  | ■                |
| Cost minimising 223Ra treatment <u>per cycle</u>               |             |                |                  | ■■■■■<br>■■■■■   |
| Resource use break down per cycle                              |             |                |                  |                  |
| - Administration procedure                                     |             |                |                  | ■■■■■            |
| - Drug acquisition (proposed effective PBS price, ex-man)      |             |                |                  | ■■■■■<br>■■■■■   |

\* Submission assumed effective ex-manufacturer price for 120 x 250 mg abiraterone tablets.

Source: sponsor submission, table 18, pp 57.

5.21 The PBAC noted that adjusting the number of cycles of abiraterone to 7.5 would change the drug acquisition cost for 223Ra to \$■■■■■.

5.22 The PBAC agreed that any costs to the health system of storing and handling 223Ra should be taken into account in the cost-minimisation calculation, noting the

information in the pre-PBAC response that the sponsor pays the costs associated with the distribution of 223Ra by the Australian Nuclear Science and Technology Organisation (ANSTO).

**Drug cost/patient/6 cycle course: \$ [REDACTED]**

5.23 The drug cost for a 6 cycle course of 223Ra is \$ [REDACTED] (\$ [REDACTED] x 6) at the requested published price.

**Estimated PBS usage & financial implications**

5.24 The submission uses a market share approach.

**Table 5: Estimated extent of radium-223 use on the PBS via substitution from other treatments**

| Year   | Year 1     | Year 2     | Year 3     | Year 4     | Year 5     | Year 6     |
|--|------------|------------|------------|------------|------------|------------|
| Projected usage for mCRPC therapies, no radium-223 listing | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Substitution to radium-223, %                              | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Estimated extent of radium-223 use                         |            |            |            |            |            |            |
| - patients   | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| - treatment cycles (= vials; 5.1 per patient)              | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |

Source: submission Table 24, pp 63

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year.

**Table 6: Estimated extent of net financial implications to the PBS / RPBS – assuming 8 abiraterone treatment cycles per patient**

| Year                                      | Year 1     | Year 2     | Year 3     | Year 4     | Year 5     | Year 6     |
|---|------------|------------|------------|------------|------------|------------|
| With no co-pay adjust                     | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| After co-pay adjust (PBS / RPBS combined) | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |

Source; submission Table 27, pp 65. All calculations based on effective cost-minimised price of radium-223.

The redacted table shows that at year 5, the estimated net saving to Government would be less than \$10 million per year.

**Table 7: Estimated extent of net financial implications to the PBS / RPBS – assuming 9.5 abiraterone treatment cycles per patient (sensitivity analysis)**

| Year                                      | Year 1     | Year 2     | Year 3     | Year 4     | Year 5     | Year 6     |
|---|------------|------------|------------|------------|------------|------------|
| With no co-pay adjust                     | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| After co-pay adjust (PBS / RPBS combined) | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |

Source: submission Table 28, pp 66 All calculations based on effective cost-minimised price of radium-223.

The redacted table shows that at year 5, the estimated net saving to Government would be less than \$10 million per year.

**Table 8: Estimated extent of net financial implications to the MBS – assuming 8 abiraterone treatment cycles per patient**

| Year   | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|--|--------|--------|--------|--------|--------|--------|
| Radium-223 administration procedures                               |        |        |        |        |        |        |
| Number of treatment cycles   | ■      | ■      | ■      | ■      | ■      | ■      |
| Total MBS costs  |        |        |        |        |        |        |
| At full benefit  | ■      | ■      | ■      | ■      | ■      | ■      |
| At 85% benefit   | ■      | ■      | ■      | ■      | ■      | ■      |
| Abiraterone-related liver function tests (cost offsets to the MBS) |        |        |        |        |        |        |
| Number of treatment cycles replaced by radium-223                  | ■      | ■      | ■      | ■      | ■      | ■      |
| Number of liver function tests reduced (X 1.54)                    | ■      | ■      | ■      | ■      | ■      | ■      |
| Total MBS costs  |        |        |        |        |        |        |
| At full benefit  | ■      | ■      | ■      | ■      | ■      | ■      |
| At 85% benefit   | ■      | ■      | ■      | ■      | ■      | ■      |
| Net MBS costs  |        |        |        |        |        |        |
| At full benefit  | ■      | ■      | ■      | ■      | ■      | ■      |
| At 85% benefit   | ■      | ■      | ■      | ■      | ■      | ■      |

Note: Please refer to the provided Section 4 spreadsheet for full details.

5.25 The submission assumes that the PBS / RPBS use of 223Ra is entirely due to substitution away from the currently available treatments.

5.26 As this is a minor submission, the utilisation estimates have not been evaluated. The savings estimated by the submission may be overestimated particularly if the published price was used for abiraterone and the effective price for 223Ra. Based on the submissions cost-minimisation approach it would be expected that the net financial implications for the PBS/RPBS/MBS would be close to zero.

### **Quality use of medicines**

5.27 The submission does not present any quality use of medicines information.

### **Financial management – Risk Sharing Arrangements**

5.28 The submission acknowledges that Risk-Sharing Arrangements (RSA) exist for cabazitaxel, abiraterone and enzalutamide.

5.29 The submission states that the sponsor would be willing to work with the Department of Health to establish an appropriate RSA for 223 Ra. However, Bayer requests a separate RSA for 223Ra and that any rebates over the cap take into account the higher costs incurred by Bayer for distributing 223Ra.

5.30 The submission cites the following example of extra costs.

- 223Ra is manufactured in Norway and is shipped to Australia as a Type A radioactive package according to international transportation guidelines for radioactive materials. It requires airfreight (\$■) due to its radioactivity (i.e., efficacy) which is depleted with a physical half-life of 11.4 days.
- Locally, 223Ra will have to be distributed by ANSTO due to its radioactive status and incurs additional pick-up (\$■) and handling fees (\$■).

- 5.31 A separate RSA with different rebate arrangements would increase the cost to Government associated with this listing.
- 5.32 While not mentioned in the submission the possibility that there may be patients requiring a grandfathering restriction would also need to be considered at the time of listing.

*For more detail on PBAC's view, see section 6 PBAC Outcome.*

## **6 PBAC Outcome**

- 6.1 The PBAC recommended the listing of radium 223Ra dichloride (223Ra) for the treatment of castration resistant metastatic carcinoma of the prostate, on a cost-minimisation basis with abiraterone.
- 6.2 The PBAC primarily relied on the MSAC's prior (April 2014) consideration of 223Ra to recommend to the Minister that 223Ra should be made available on the PBS under a Section 100 special arrangement for radiopharmaceuticals.
- 6.3 The PBAC considered that abiraterone was the appropriate comparator, noting that abiraterone was itself partially cost-minimised to cabazitaxel and that enzalutamide was cost-minimised to abiraterone. The PBAC accepted the submission's clinical claims, including superior safety over cabazitaxel for some patients.
- 6.4 The PBAC noted that the proposed restriction is consistent with that previously recommended by the MSAC, and advised that the following additional criteria be added to the PBS restriction:
- The patient must have two or more skeletal metastases,
  - The patient must not receive PBS-subsidised 223Ra if progressive disease develops while on 223Ra,
  - The patient must not have received prior treatment with abiraterone or enzalutamide, OR
- The patient must have developed intolerance to enzalutamide requiring permanent withdrawal
- AND
- The patient must have developed intolerance to abiraterone requiring permanent withdrawal.

The PBAC considered it may also be appropriate to restrict prescribing to specialists in nuclear medicine and requested the issue of who is appropriate to prescribe be considered as part of the development of the S100 arrangement.

- 6.5 The PBAC noted the pre-PBAC response request that patients be allowed to access 223Ra and enzalutamide or abiraterone sequentially. The PBAC agreed that there may be some patients who would benefit from sequential use and noted the sponsor's comment that comparative RCT data to support sequential use is unlikely to be forthcoming. However, the 223Ra submission requests listing at the same cost per course as abiraterone and enzalutamide, and the PBAC recalled that when it

recommended enzalutamide on a cost-minimisation basis to abiraterone in November 2014, it had advised it would be inappropriate to allow sequential use of abiraterone and enzalutamide in the absence of evidence of effectiveness. The PBAC considered that substantial price reductions across all agents would be required for it to consider allowing sequential use.

- 6.6 The PBAC advised that the restrictions for both abiraterone and enzalutamide should be updated to specify that patients must not have received prior treatment with 223Ra.
- 6.7 The PBAC did not support the sponsor's request for a separate RSA. The PBAC acknowledged that 223Ra has higher shipping and distribution costs; however, it did not consider that this was a reason for it not to join the current RSA with abiraterone and enzalutamide.
- 6.8 The PBAC noted advice from the Department that there were numerous steps involved in developing a new Section 100 program for radiopharmaceuticals, based on specific issues related to the radioactive nature of the product, which could delay the progression of the recommendation to Ministerial consideration.
- 6.9 The PBAC advised that 223Ra is not suitable for prescribing by nurse practitioners as Section 100 listings are not currently included for prescribing by nurse practitioners.
- 6.10 The PBAC recommended that the Early Supply Rule should not apply, as it has not previously been applied to Section 100 HSD listings. A policy decision will need to be made as to whether this rule will be applied to any future Section 100 radiopharmaceuticals program.
- 6.11 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## **7 Recommended listing**

Public Summary Document – November 2017 PBAC Meeting

7.1 Add new item (Draft restriction only shown below):

| Name, restriction, manner of administration, form         | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Proprietary name and manufacturer |
|---|--------------------------|--------------------------|----------------|-----------------------------------|
| RADIUM-223, 6mL/20 mL vial (6 MBq)a for IV administration | 1                        | 1                        | 5              | XOFIGO, Bayer Australia Ltd       |

|                                |  |
|--------------------------------|--|
| <b>Category/Program</b>        | Section 100 – new program (name to be confirmed)   |
| <b>PBS Indication:</b>         | Castration resistant metastatic carcinoma of the prostate  |
| <b>Restriction:</b>            | <input checked="" type="checkbox"/> Authority Required - In Writing<br><input checked="" type="checkbox"/> Authority Required – Telephone  |
| <b>Clinical criteria:</b>      | <p>Patients must have <math>\geq 2</math> skeletal metastases<br/>           AND<br/>           Patient must have a WHO performance status of 2 or less<br/>           AND<br/>           Patient must have failed treatment with docetaxel due to resistance or intolerance; OR<br/>           Patient must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel<br/>           AND<br/>           The treatment must not be used in combination with chemotherapy.<br/>           AND<br/>           The patient must not receive PBS-subsidised 223Ra if progressive disease develops while on 223Ra<br/>           AND<br/>           The patient must not have received prior treatment with abiraterone or enzalutamide; OR<br/>           The patient must have developed intolerance to enzalutamide requiring permanent withdrawal<br/>           AND<br/>           The patient must have developed intolerance to abiraterone requiring permanent withdrawal.</p> |
| <b>Prescriber Instructions</b> | A maximum of six (6) intravenous injections are to be administered at four-weekly intervals.   |
| <b>Administrative Advice</b>   | <p>Special Pricing Arrangements apply.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>At the pre-calibrated reference date of 14 days, the radioactive concentration is 1000 kilobecquerels (kBq)/mL. If administered on a day other than the reference date, the volume is adjusted according to the physical decay table supplied with each shipment.</p>   |

7.2 Amend existing listings as follows:

*Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.*

| Name, restriction, manner of administration, form | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Proprietary name and manufacturer |
|---|--------------------------|--------------------------|----------------|-----------------------------------|
| ABIRATERONE<br>250 mg tablet, 120                 | 1                        | 120                      | 2              | ZYTIGA, Janssen-Cilag Pty Ltd     |
| ABIRATERONE<br>500 mg tablet, 60                  | 2                        | 120                      | 2              |                                   |

|                              |  |
|------------------------------|--|
| <b>Category/Program</b>      | General Schedule – (Code GE)   |
| <b>PBS Indication:</b>       | Castration resistant metastatic carcinoma of the prostate  |
| <b>Restriction:</b>          | <input checked="" type="checkbox"/> Authority Required - In Writing<br><input checked="" type="checkbox"/> Authority Required – Telephone  |
| <b>Clinical criteria:</b>    | The treatment must be used in combination with a corticosteroid<br>AND<br>Patient must have a WHO performance status of 2 or less<br>AND<br>Patient must have failed treatment with docetaxel due to resistance or intolerance; OR<br>Patient must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel<br>AND<br>The treatment must not be used in combination with chemotherapy.<br>AND<br>The patient must not receive PBS-subsidised abiraterone if progressive disease develops while on abiraterone<br>AND<br>The patient must not have received prior treatment with <i>radium 223Ra</i> or enzalutamide; OR<br>The patient must have developed intolerance to <i>radium 223Ra</i> or enzalutamide of a severity necessitating permanent withdrawal |
| <b>Administrative Advice</b> | Special Pricing Arrangements apply.  |

| Name, restriction, manner of administration, form | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Proprietary name and manufacturer         |
|---|--------------------------|--------------------------|----------------|---|
| ENZALUTAMIDE, 40 mg capsule, 112                  | 1                        | 112                      | 2              | XTANDI, Astellas Pharma Australia Pty Ltd |

|                              |   |
|------------------------------|---|
| <b>Category/Program</b>      | General Schedule – (Code GE)  |
| <b>PBS Indication:</b>       | Castration resistant metastatic carcinoma of the prostate   |
| <b>Restriction:</b>          | <input checked="" type="checkbox"/> Authority Required - In Writing<br><input checked="" type="checkbox"/> Authority Required – Telephone   |
| <b>Clinical criteria:</b>    | Patient must have a WHO performance status of 2 or less<br>AND<br>Patient must have failed treatment with docetaxel due to resistance or intolerance; OR<br>Patient must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel<br>AND<br>The treatment must not be used in combination with chemotherapy.<br>AND<br>The patient must not receive PBS-subsidised this drug if progressive disease develops while on this drug<br>AND<br>The patient must not have received prior treatment with abiraterone or <i>radium 223Ra</i> ; OR<br>The patient must have developed intolerance to abiraterone or <i>radium 223Ra</i> of a severity necessitating permanent treatment withdrawal |
| <b>Administrative Advice</b> | Special Pricing Arrangements apply.<br><br>No increase in the maximum number of units may be authorised.<br><br>No increase in the maximum number of repeats may be authorised.   |

## 8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## 9 Sponsor's Comment

Bayer welcomes the PBAC positive recommendation for listing of Xofigo (radium-223) on the PBS which re-affirms the positive MSAC recommendation from April 2014. Bayer also welcomes the commitment from Government to enable a pathway to funding radium-223 via the development of a new Section 100 program for therapeutic radiopharmaceuticals.

Bayer is looking forward to working with the Department in establishing the new program, in order to provide Australian patients with access to Xofigo (radium-223) in a timely manner.