Cost Effectiveness of radium-223 (Xofigo®) for castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases.

The NCPE has issued a recommendation regarding the use of radium-223 for this indication. The NCPE does not recommend reimbursement of radium-223 at the submitted price.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the manufacturer's (Bayer) economic dossier on the cost effectiveness of radium-223. The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits that the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examine all the evidence that may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics ***December 2014***

Summary

Bayer submitted a dossier for radium-223 (Xofigo®) on 8th April 2014. Following preliminary review, final amendments to the submission were received in October 2014. Xofigo® is indicated for castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases. It is a hospital-only product licensed as a course of six intravenous injections given at four-week intervals. Xofigo® contains radium-223, a calcium mimetic which accumulates in areas of bone that have a high turnover, for example, where bone metastases develop. Once bound to bone, the drug emits low levels of radiation that travel at a short-range, thereby limiting damage to nearby tissue.

1. Comparative Effectiveness

- Two comparators were presented in the pharmacoeconomic evaluation. First, radium-223 was compared to best supportive care alone in patients who had received docetaxel or could not receive docetaxel. As abiraterone acetate (abiraterone), an oral treatment for metastatic castration-resistant prostate cancer, has recently been approved for use in patients who have received docetaxel, the NCPE also considered abiraterone as a comparator. Therefore, as the second comparison, Radium-223 was compared to abiraterone 1,000mg once daily in combination with prednisolone 10mg/day in patients with metastatic castration-resistant prostate cancer who have received prior docetaxel based chemotherapy.
- The evidence submitted to support the efficacy of radium-223 was based on the phase III clinical trial 'ALSYMPCA', which compared radium-223 plus best supportive care to best supportive care alone (N Engl J Med 2013; 269:213-223). Patients who had castration resistant prostate cancer with at least two bone metastases but no known visceral metastases were included in this trial (n=921) and were randomly assigned to receive either radium-223 (six intravenous injections at four-weekly intervals) or best supportive care. The primary endpoint for this trial was overall survival. Secondary endpoints included time to first symptomatic skeletal event (e.g. spinal cord compression, lower extremity weakness, pathological bone fracture) and time to progression, as determined by blood test levels of (i) total alkaline phosphatase (ALP) progression, (ii) prostate

specific antigen (PSA) progression. Median overall survival was 14.9 months in the radium-223 group versus 11.3 months in the placebo group (hazard ratio 0.70, 95% confidence interval 0.58, 0.83). Median time to first symptomatic skeletal-related event was 15.6 months in the radium-223 group versus 9.8 months in the placebo group. The median time to progression (as measured by either ALP or PSA) was longer in the radium-223 group than the placebo group.

- An indirect comparison was performed to establish the relative efficacy of radium-223 versus abiraterone. Information on efficacy of the comparator abiraterone was taken from the phase III clinical trial COU-AA-301 (N Engl J Med 2011; 364; 1995-2005), which examined abiraterone in patients who had previously received docetaxel. No comparison of radium-223 to abiraterone could be performed in patients who had not received docetaxel as the relevant clinical trials were not comparable. Regarding the comparison of evidence in ALSYMPCA and COU-AA-301, these trials also had important differences; unlike ALSYMPCA, COU-AA-301 included patients with visceral metastases as well as patients with skeletal metastases. Also, relative efficacy estimates could only be calculated for the outcomes of overall survival and progression-free survival; data was unavailable for the outcome of symptomatic skeletal-event free survival.

  The results of the indirect comparison found no significant difference in the efficacy of radium-223 versus abiraterone regarding effects on survival (hazard ratio: 0.96, 95% credible interval 0.73, 1.26) or on progression-free survival as measured by PSA (hazard ratio: 1.02, 95% credible interval 0.78, 1.33); a relative effect on progression-free survival as measured by ALP could not be calculated in the comparison to abiraterone due to lack of available data.

2. Safety

- In the ALSYMPCA trial Radium-223 demonstrated a favourable safety profile. Adverse events which had a notably higher frequency in the radium-223 group than the placebo group included diarrhoea (25.2% versus 15.0%), thrombocytopenia (11.5% versus 5.6%) and neutropenia (5.0% versus 1.0%) but commonly reported adverse events (e.g. anaemia, nausea) were observed at a similar rate in the radium-223 and placebo groups. Two percent of patients in the

radium-223 group experienced bone marrow failure (versus none in the placebo group); 54% of these patients required blood transfusions. The company has committed to post-marketing studies of the long-term safety of radium-223.

3. Cost-Effectiveness analysis

- A cost utility analysis comparing radium-223 to (i) best supportive care and (ii) abiraterone (post docetaxel population only) was submitted by the company. The perspective of the HSE (payer) was presented.

- A Markov state-transition model was used to describe the progression of patients through health states following receipt of radium-223 or the comparator. The model contained five health states and had a cycle length of one week. Patients entered the model in the 'progression-free survival without symptomatic skeletal event (SSE)' health state. At the end of each cycle, patients could remain in that state or could move to one of the other four states: progression-free survival with SSE, progression without SSE, progression with SSE, or death. Progression was based on surrogate markers which included ALP for the comparison with best supportive care and PSA for the comparison to abiraterone.

- Health benefits were measured in quality-adjusted life years (QALYs) and disutilities associated with adverse events were included. Costs included drug acquisition and administration, costs of disease management (supportive therapies, medical procedures and tests, medical vists), costs of adverse event management, costs of symptomatic skeletal event management and costs of subsequent lines of treatment following receipt of radium-223 or comparator.

Results

The model results presented to the NCPE incorporated a 4% manufacturer's rebate which does not apply to radium-223 due to its hospital-only status. The NCPE review group therefore removed this rebate from calculations relevant to radium-223 and also

applied half cycle correction within the model. Results presented below also include the costs associated with receipt of further treatments (e.g. receipt of enzalutamide or abiraterone subsequent to treatment with radium-223), which was assumed to occur in approximately 15% of patients. It should be noted that corresponding efficacy data for the receipt of such sequential treatment was not available.

Radium-223 versus best supportive care (based on overall trial population data)

This comparison was conducted using data from the overall results of the ALSYMPCA trial (full trial population) and resulted in an incremental cost-effectiveness ratio (ICER) of €79,948. As such, radium-223 was not found to be cost effective at a threshold of €45,000/QALY. The NCPE also examined the effect on the ICER of the full licensed course of radium-223 injections being administered (as opposed to 5.1 injections, the mean number received in ALSYMPCA). Under this input the ICER was found to increase to €93,185.

Radium-223 versus abiraterone (based on post-docetaxel population trial data)

This comparison was conducted using data derived from an indirect comparison analysis. Data for efficacy of radium-223 comprised data from patients within the ALSYMPCA trial who had first received docetaxel. Data on the efficacy of abiraterone was taken from the COU-AA-301 trial of abiraterone versus placebo in patients who had first received docetaxel. Due to lack of data, no comparison in the pre-docetaxel population could be performed. The model inputs presented by the company suggested that radium-223 was associated with lower costs than abiraterone and presented a minimal incremental QALY gain (0.018 QALY). As such, under these inputs radium-223 was deemed cost effective relative to abiraterone at a threshold of €45,000/QALY.

The review group varied two additional model parameters to comply with NCPE preferred model inputs. These included: (i) calculation of radium-223 drug costs based on receipt of the full licensed course of treatment (6

injections) as opposed to the mean number of injections received in the clinical trial (5.1 injections); (ii) inclusion of a reduction in the price of the comparator abiraterone similar to that which is estimated to be currently in place. Under these circumstances, radium-223 was not found to be cost effective when compared to abiraterone (Incremental cost-effectiveness ratio: €80,361/QALY).

Sensitivity analysis

- A one way sensitivity analysis (OWSA) performed under the NCPE preferred model inputs (see above) found that the cost effectiveness of radium-223 relative to best supportive care was highly sensitive to the time horizon. Given a time horizon of 2 years as opposed to the base case of 10 years, the incremental cost per QALY gained rose from €79,948 to €129,448. The cost effectiveness of radium-223 relative to abiraterone was mainly sensitive to the mean number of weeks of treatment with abiraterone. Given 22 weeks of treatment (base case: 32), the ICER rises to €361,611/QALY; at 42 weeks of abiraterone treatment radium-223 dominates abiraterone (ICER: -€474,468/QALY). The ICER for radium-223 versus abiraterone was also sensitive toto the health state utility values.

- The probability of cost effectiveness of radium-223 versus best supportive care (using the NCPE preferred model inputs) is 0% at a threshold of €45,000/QALY. The probability of cost effectiveness of radium-223 versus abiraterone (post-docetaxel setting) was found to be 41%.

4. Budget Impact Analysis

Considering patients who have and have not received prior docetaxel, the company estimates a total of 134 patients eligible for treatment with radium-223 in the year 2014, rising to 139 in the year 2018. These figures were arrived at by application of prostate cancer epidemiology statistics from the scientific literature against a background of overall National Cancer Registry Ireland prostate cancer incidence figures.

The annual treatment cost of acquiring and administering a full treatment course of radium-223 (6 injections in total administered at four-weekly intervals) is estimated as €33,679. The gross budget impact of radium-223 acquisition and administration is estimated to be approximately €740,000 for the year 2014 rising to approximately €1,776,000 in 2018.

Considering both pharmacy costs (including costs of radium-223, abiraterone and best supportive care treatments) and non-pharmacy costs (e.g. prostate cancer management, management of adverse events, management of symptomatic skeletal events and the costs of subsequent therapies), the net budget impact to the HSE of introducing radium-223 is estimated at approximately €714,000 for the year 2014 rising to €1,642,000 in 2018. This represents a cumulative 5-year budget impact of approximately €5,900,000.

5. Conclusion

Bayer submitted a dossier for Radium-223 (Xofigo®) on 8th April 2014. Radium-223 is indicated for castration-resistant prostate cancer in patients with bone metastases and no known visceral metastases. Following NCPE assessment of the company submission, the NCPE considers that the cost effectiveness of radium-223 has not been demonstrated.