NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Radium-223 dichloride for treating metastatic hormone relapsed prostate cancer with bone metastases

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: National Cancer Research Institute/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology

Comments coordinated by Dr Isabel Syndikus

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

  Dr Syndikus is a member of the Prostate Clinical Studies Group of the NCRI, a member of the work stream 3 Clinical and Translational Radiotherapy Research Working Group a Fellow of both the RCP and RCR.

- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The following groups of patients with prostate cancer are treated with androgen deprivation (hormone) therapy: short-term therapy combined with radiotherapy for intermediate (6 months) or high risk locally advanced disease (3 years). Patients with advanced disease (metastasis beyond the prostate) or relapse after local treatment are treated with lifelong therapy. Patients can chose either between medical or surgical castration. There is same geographical variation, but most men choose medical therapy.
Monthly or 3 monthly injections of gonadotrophin-releasing hormone (GnRH) agonists are widely used which are also called luteinizing hormone-releasing hormone agonists (LHRH). Currently goserelin, leuporelin and triptorelin are licensed in the UK. There are cost differences between the different drugs, but the therapeutic effects and side effect profiles are similar.
The GnRH agonists stimulate initially the LHRH receptors and cause a (transient) testosterone surge; hence they are combined with cyproterone actate, flutamide or bicalutamide for the first 4 weeks. These drugs block the androgen receptors on a cellular level. The flare might lead to an exacerbation of bone pain, obstructive outflow symptoms and possible the development of urinary retention or cord compression. In clinical practice this is rare and most patients improve with treatment quickly. The use of GnRH agonists is discussed in the NICE clinical guidelines 58.
A nonsteroidal anti-androgen, bicalutamide is used as an alternative for patients without metastatic disease. It has the advantage of reduced hot flushes and improved libido; there is a lower risk of cardiovascular events and osteoporosis. Patients have more problems with gynecomastia (breast enlargement) and nipple

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pain. Bicalutamide monotherapy is not licensed for patients with metastatic disease as it has an adverse effect on overall survival. However, for patients with several cardiovascular risk factors this adverse effect is overshadowed by a significantly increased cardio-vascular mortality because of GnRH agonists therapy.
Degarelix is a direct GnRH antagonist blocking the receptors and induces a rapid suppression of testosterone without a flare. It might have additional advantages for patients who are very symptomatic with a impending cord compression or have significant bone pain. These patients are normally treated additionally with high dose steroids which also suppress the pituitary LHRH surge and/or radiotherapy. Surgical castration is not a realistic option as these patients tend to be very ill and a further surgical procedure should be avoided if possible. There is evidence that obstructive urinary symptoms improve better with Degarelix, hence reducing follow on treatment costs.
In some secondary care hospital it is possible to prescribe Degarelix for this subgroup of patients. Cardiovascular toxicity and other side effects are similar to GnRH agonists

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The administration of Degarelix is by monthly sc injection and can be provided in the primary care setting, similar to GnRH agonists. Patients need to be monitored for disease progression, urinary outflow obstructive symptoms, cardiovascular risk factors, obesity, diabetes and osteoporosis. The duration of GnRH agonists or Degarelix is the same; in the advanced disease setting, therapy is continued even if PSA or symptomatic diseases progression is observed (hormone relapsed disease). Additional therapies (chemotherapy, second line hormones or other supportive

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treatments are given as per NICE clinical guidelines 58. For suitable patients intermitted GnRH agonists therapy can be used. There are no data regarding this available for Degarelix, but as the drugs are fairly similar, this could be an option for suitable patients.

Outcome
PSA response: In the phase III study of Klotz et al (n=610), PSA relapse rates are significantly higher on GnRH agonists compared to Degarelix. The trial patients had had Patients in the control group were crossed over after the first year if they had not relapsed and randomised to 2 different dose levels. The reduced relapse rate was also observed in the cross over group.
Survival: The study was not powered to evaluate the effect of Degarelix on survival. The overall mean survival in the control arm for the metastatic STAMPEDE arm is around months. It might well be that in this group of patients Degarelix could have a beneficial effect. In the Klotz study, only 20% of patients had metastatic disease and patients in the leuporeline arm were crossed over to Degarelix after year 1 (n=120). Patients with metastatic disease would be most likely to benefit from better PSA control and this could translate in increased survival. The numbers are too small to analyse this.
Quality of life: Symptomatic patients may achieve a earlier a better symptom control, both for localised and advanced disease.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

There are no concerns regarding equality of access for disabled patients or racial groups

Any additional sources of evidence

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Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

no

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The costs of administration might be higher because of a monthly depot injection is required. Other logistic considerations are similar to GnRH agonists.