NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Padeliporfin for untreated localised prostate cancer

1 Recommendations

1.1 Padeliporfin is not recommended, within its marketing authorisation, for untreated, unilateral, low-risk prostate cancer in adults.

1.2 This recommendation is not intended to affect treatment with padeliporfin that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatments for low-risk prostate cancer include active surveillance and, for people whose disease has progressed (usually beyond low-risk disease), radical therapies such as surgery and radiotherapy. Focal therapies such as cryotherapy and high-intensity focused ultrasound can also be used, but are not routinely available.

Professional organisations and NHS England say that there is a growing trend for people with low-risk disease to have active surveillance rather than radical therapy. This is because long-term studies show that people with low-risk disease live as long whichever they have, but radical therapies are associated with long-term, severe side effects. Also,

improvements in diagnostic tests mean that low-risk disease can be more accurately identified.

The company proposes padeliporfin as an option for people with low-risk disease who choose not to have active surveillance and so would otherwise have radical therapies. There is no clinical evidence on how effective padeliporfin is at slowing the disease compared with radical therapies. Also, there is no evidence to support the company's assumption that the length of time people live with padeliporfin is the same as with radical therapies.

Clinical trial evidence comparing padeliporfin with active surveillance does show that, at 2 years, it is more effective at slowing prostate cancer. However, it is unclear whether the benefit seen at 2 years leads to people living longer. Also, it is unclear whether some of the people in the trial would have had intermediate-risk prostate cancer.

Professional organisations and NHS England do not support using padeliporfin for low-risk prostate cancer because, like radical therapies, it is associated with long-term side effects, without supporting evidence of long-term clinical benefit.

The company's cost-effectiveness analyses compare padeliporfin with radical therapies. However, because there is no clinical-effectiveness evidence comparing padeliporfin and radical therapies, it is not possible to consider these analyses. Therefore, padeliporfin cannot be recommended for untreated, unilateral, low-risk prostate cancer.

2 Information about padeliporfin

Marketing authorisation indication	Padeliporfin (Tookad, Steba Biotech) is indicated as monotherapy for 'adults with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy of at least 10 years and: • clinical stage T1c or T2a • Gleason score no more than 6, based on high-resolution biopsy strategies • prostate-specific antigen (PSA) no more than 10 ng/ml • 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1 to 2 positive cancer cores with at least 50% cancer involvement in any 1 core or a PSA density of at least 0.15 ng/ml/cm^3'
Dosage in the marketing authorisation	The recommended dose, given intravenously is a single dose of 3.66 mg/kg of padeliporfin, given using a vascular-targeted photodynamic therapy procedure.
Price	The list price of padeliporfin is £3,761 per 183 mg vial (excluding VAT; company submission). The average cost of treatment is £12,111 per patient (including consumables and leasing the laser; excluding VAT; company submission). The company has a commercial arrangement, which would apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Steba Biotech and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Diagnosing prostate cancer and risk stratification

New diagnostic techniques for prostate cancer are more accurate at identifying low-risk disease

3.1 NICE's clinical guideline on prostate cancer considers tumours to be low-risk if the following criteria are met: serum prostate-specific antigen (PSA) no more than 10 ng/ml, a Gleason score no more than 6, and a clinical stage of T1 to T2a. [The Gleason Score is a grading system that rates the aggressiveness of the 2 largest area of prostate cancer cells in a tumour. Each area is scored on how healthy it looks, so healthy tissue scores 1

or 2 and abnormal tissue scores 3]. The clinical experts explained that the techniques used to diagnose prostate cancer in the NHS are changing, for example, transrectal ultrasound (TRUS) guided biopsy is being replaced by multi-parametric magnetic resonance imaging (MRI). MRI techniques are more accurate at differentiating low-risk disease that does not need treatment, from disease that is likely to progress. In response to consultation, professional organisations confirmed that over the past 5 years, in line with guidance issued by NHS England, everyone with an elevated PSA level should be offered pre-biopsy multi-parametric MRI as the first diagnostic test, followed by MRI-targeted biopsy. They confirmed that misclassification of low-risk disease is much lower because multi-parametric MRI can identify 90% of significant cancers compared with about 50% identified by TRUS-guided biopsy alone. The committee was aware that the NICE prostate cancer guideline is currently updating the diagnostic criteria. It agreed that the main technique used to initially diagnose low-risk prostate cancer in the NHS is multi-parametric MRI.

Treatment pathway for localised prostate cancer

Low-risk disease is usually managed with active surveillance to prevent over-treatment with radical or focal therapies

3.2 The clinical experts explained that in practice, active surveillance (that is, monitoring for disease progression without an active treatment) is usually offered to people with low-risk disease in line with recommendations in NICE's clinical guideline on prostate cancer. The committee understood that active surveillance in the NHS includes multi-parametric MRI (if not already done), regular serum PSA testing and kinetics, digital rectal examinations and re-biopsy. The aim of encouraging active surveillance is to avoid over-treatment of disease that is unlikely to progress or shorten people's lives (given the long-term, severe adverse events associated with treatment). Clinicians generally only offer patients radical therapies including prostatectomy (surgery), external beam radiotherapy and brachytherapy if the disease progresses to intermediate-risk. One clinical

expert explained that there are 4 ways to move from active surveillance to radical therapies: patients no longer wish to stay on active surveillance (surveillance fatigue), increasing PSA levels (biochemical progression), increase in risk of disease progression, or increase in clinical stage (such as from T2a to T2b). If patients have radical therapy, surveillance continues with less intensive monitoring specific to the type of radical therapy. Professional organisations and NHS England have confirmed that current practice manages low-risk disease with active surveillance. Low-risk disease is unlikely to progress and clinical trial evidence has shown no difference in cancer-specific or overall survival whether people have radical therapies or active surveillance. Also, large prospective cohort studies have shown that in the medium to long-term, people on active surveillance have low mortality rates. Therefore, people with low-risk disease are now choosing to be monitored rather than have active treatment with radical or focal therapies which have unwanted side effects. The NHS England Cancer Drug Fund clinical lead explained that the main reason for this trend is the growing confidence that the diagnostic techniques accurately identify low-risk disease (see section 3.1). The committee concluded that low-risk disease is usually managed with active surveillance in the NHS.

There is variation in access to current focal therapies in the NHS

3.3 The clinical experts explained that padeliporfin is a type of focal therapy that targets the main lesion, rather than the whole prostate. The committee was aware that NICE's interventional procedures guidance recommend cryotherapy and high-intensity focused ultrasound for localised prostate cancer only under special arrangements. NICE's clinical guideline on prostate cancer recommends these options only in a clinical trial setting. The committee was aware that NICE made these recommendations in 2012 and 2008, and that the evidence for these focal therapies may have progressed. The clinical experts explained that focal therapy is used as an alternative to radical therapy for clinically significant disease or for patients with low-risk disease who choose not to have

active surveillance. It is not used when there are no clinical indications suggesting disease progression because of concerns about long-term side effects and a lack of evidence about long-term survival benefits. In response to consultation, NHS England stated that focal therapies are usually used to treat intermediate- or high-risk prostate cancer in the UK. It also highlighted that the UK Focal Therapy Users Group had issued guidance that focal therapy should be used only in intermediate-risk disease. It should not be used as an alternative to active surveillance in disease that is unlikely to progress. The committee concluded that focal therapies are not routinely available in the NHS, but when they are used, it is to treat intermediate- or high-risk disease, which is not included in the marketing authorisation for padeliporfin (see section 2).

Positioning of padeliporfin in the treatment pathway

There is little unmet need for a new treatment such as padeliporfin for people with low-risk disease

3.4 The company explained that padeliporfin is not an alternative to active surveillance for clinically insignificant disease (that is, disease that has little to no chance of progression in a person's expected lifetime and which is unlikely to benefit from active treatments; see sections 3.1 and 3.2). It suggested that padeliporfin might be an option for people with low-risk disease who choose not to have active surveillance either at diagnosis or after a period of active surveillance (surveillance fatigue), but before radical therapies. It highlighted that studies suggest about 30% to 65% of people with low-risk disease choose to have radical therapy. However, the committee noted that more recent data from the 2015 to 2016 National Prostate Cancer Audit showed that only 8% of people had radical therapy for low-risk disease, likely related to improved diagnostic techniques (see sections 3.1 and 3.2). It also noted that clinicians are unlikely to offer active treatment to people with low-risk disease without disease progression (see section 3.2). The committee considered that padeliporfin would not be appropriate for people with surveillance fatigue

because the company had confirmed that surveillance continues after padeliporfin. In response to consultation, the company explained that active surveillance after padeliporfin is different to active surveillance without treatment. Professional organisations agreed with the company that treatment of low-risk disease may address patients' anxiety about not having any treatment for their cancer. However, they highlighted that survival rates with active surveillance are high (98.8% at 10 years in the ProtecT trial). The committee concluded that there is little unmet need for a new treatment such as padeliporfin for people with low-risk disease.

Comparators

Relevant comparators are radical therapies

3.5 The company considered that, given the proposed position of padeliporfin in the treatment pathway, the most appropriate comparators are radical therapies (including prostatectomy, external beam radiotherapy and brachytherapy). The committee noted that other focal therapies are not routinely available in the NHS but where available, are normally used to manage intermediate- or high-risk disease (see section 3.3). Therefore, it agreed that focal therapies could not be considered comparators. It concluded that although there is little unmet need for additional treatments at this stage of the treatment pathway, the relevant comparators are radical therapies.

Clinical evidence

The key clinical evidence comes from a subgroup of 1 trial comparing padeliporfin plus active surveillance with active surveillance alone

3.6 The evidence for padeliporfin came from a subgroup of the PCM301 trial, a phase 3, multi-centred, randomised, open-label, parallel group study. It compared padeliporfin plus active surveillance with active surveillance alone in 413 adults with untreated, low-risk prostate cancer. The subgroup had 158 patients with unilateral, low-risk but not very-low-risk prostate cancer. The co-primary outcomes at 24 months were absence of definitive

cancer and treatment failure, defined as histological cancer progression from low- to intermediate or high-risk or prostate cancer-related death.

The patients in the PCM301 subgroup are likely to be different to those seen in the NHS

3.7 The committee noted that the diagnostic techniques used in PCM301 (TRUS-guided biopsy) are different to those currently used in the NHS (multi-parametric MRI; see section 3.1). In response to consultation, professional organisations highlighted that these differences in diagnostic techniques mean that some patients in PCM301 were likely to be misclassified as having low-risk disease when they would have been identified as having higher risk disease in the NHS. The committee agreed that the patients in the PCM301 subgroup may not reflect patients with low-risk disease likely to be seen in the NHS. It is therefore unlikely that the trial results are generalisable to NHS patients.

The treatment failure end point used in PCM301 has no proven relationship to longer-term survival outcomes

3.8 The committee noted that, in patients randomised to padeliporfin plus active surveillance, there were higher rates of absence of definitive cancer and absence of disease progression compared with active surveillance alone (see table 1). The ERG noted that disease progression was higher in the active surveillance group in PCM301 (58%) compared with other trials. For example, ProtecT, a UK-based, randomised controlled trial on prostatectomy and external beam radiotherapy that mainly recruited people with low- and intermediate-risk disease from 1999 to 2009 (77% of people had a Gleason score of 6). This study reported that 30% of patients in the active surveillance group had disease progression. The company explained that patients in PCM301 had re-biopsies at 12 months and 24 months, while ProtecT did not have any planned re-biopsies. It suggested that these planned biopsies in PCM301 led to earlier detection of disease progression. In response to consultation, professional organisations highlighted that because of the misclassification errors

associated with TRUS-guided biopsies, higher risk disease missed at the baseline screening in PCM301 (see section 3.7) may have been correctly identified at the re-biopsies. As such, some people meeting PCM301's disease progression end point may not have done so because of biological progression. While this misclassification bias would apply to both arms of PCM301, the committee agreed that it is likely that the trial overestimated the absolute difference in treatment effect for low-risk disease. Also, the professional organisations explained that the absence of disease progression end point used in PCM301 has no proven relationship to longer-term survival outcomes. The committee concluded that although padeliporfin plus active surveillance is more likely to achieve the trial end point compared with active surveillance alone in the short term, any benefit and long-term effectiveness with respect to length and quality of life are uncertain. Also, it is unclear that there would be lower rates of disease progression with padeliporfin than with active surveillance in NHS clinical practice because fewer patients are likely to have their cancer misclassified as low-risk under current diagnostic techniques (see section 3.1).

Table 1 Co-primary end points for PCM301 subgroup at 24 months

Outcomes	Padeliporfin plus active surveillance (n=80, unless otherwise stated)	Active surveillance alone (n=78, unless otherwise stated)	Risk ratio (95% confidence intervals)
Absence of definitive cancer at 24 months			
Lobe diagnosed at baseline	71%	15%	4.6 (2.7 to 7.9)
Whole gland	45%	10%	4.4 (2.2 to 8.3)
Absence of disease progression[a] at 27 months			
Lobe diagnosed at baseline	90% of 71 patients	42% of 67 patients	2.2 (1.6 to 2.9)[b]
Whole gland	64% of 76 patients	25% of 71 patients	not available
[a] no prostate cancer-related deaths in study; [b] calculated by ERG			

There is no clinical evidence from the company comparing padeliporfin with radical therapies

3.9 The company explained in its submission that it could not indirectly compare padeliporfin and radical therapies. This was because of the different outcomes reported in the trials and those used in its economic model, such as time to radical therapy. The ERG agreed with the company that a network meta-analysis was not possible given the available evidence. The committee noted that the company had not presented any evidence compared with focal therapies (see section 3.3), that might have allowed an indirect comparison with radical therapies. In response to consultation, the company stated that biochemical recurrence studies (increase in serum PSA levels) have shown that at 3 years, 87% of people having prostatectomy and 95% of people having radiotherapy had biochemical disease-free survival. But, in PCM301, 90% of people having padeliporfin had no disease progression, based on increasing Gleason score, tumour volume or PSA levels, or advanced disease at 2 years. The company did not provide any analyses comparing the clinical effectiveness of padeliporfin with radical therapies. The committee agreed that it had not seen any evidence of the effectiveness of padeliporfin compared with radical therapies, the only relevant comparator (see

section 3.5). It also recognised that radical therapies are rarely offered to people with low-risk disease in the NHS, the only population for which padeliporfin is licensed for use. During consultation, professional organisations highlighted that padeliporfin "should not be recommended for use in the UK for this indication" and that they did not consider padeliporfin would advance patient care. The committee agreed that it could not conclude whether padeliporfin offered any clinical benefit compared with radical therapies.

Adverse events

Adverse events such as sexual and bowel dysfunction may be lower with padeliporfin than with radical therapies

3.10 The committee noted that the rates of sexual and bowel dysfunction were much higher in the padeliporfin plus active surveillance group than in patients having active surveillance alone. The clinical experts explained that radical therapies are associated with higher rates of bowel, urinary and sexual dysfunction than those seen in patients having padeliporfin in PCM301. The committee was aware that no long-term evidence on the adverse effects of padeliporfin was available. The committee concluded that a likely clinical benefit of padeliporfin is a lower risk of having these adverse events than with radical therapies, but agreed that it had not seen any supporting evidence (see section 3.9).

Company's economic model

It is not appropriate to consider padeliporfin's cost effectiveness compared with radical therapies because the relative clinical effectiveness is unknown

3.11 The committee recalled that the company did not present any clinical evidence comparing padeliporfin with radical therapies (see section 3.9). It noted that the clinical benefit of padeliporfin in terms of oncological or survival outcomes and quality of life compared with radical therapies was unknown. Survival with padeliporfin was assumed to be the same as with radical therapies. However, given that there was no relative clinical-

effectiveness evidence and the short duration of the padeliporfin trial (2 years), the committee could not assess whether this was a reasonable assumption. The committee acknowledged that the company had revised its economic model to consider some of the committee's preferences in the appraisal consultation document. However, the committee agreed that, because it had seen no evidence of the relative clinical effectiveness of padeliporfin compared with radical therapies, it could not consider the cost-effectiveness analyses.

Conclusion

Padeliporfin is not recommended for use in the NHS for untreated, unilateral, localised, low-risk prostate cancer

3.12 The committee recalled the comments from NHS England and the professional organisations that padeliporfin should not be recommended for use in the NHS for this indication, and that over-treatment of low-risk prostate cancer should be discouraged because it is unlikely to progress (see section 3.2). It concluded that it could not recommend padeliporfin for use in the NHS for untreated, unilateral, localised, low-risk prostate cancer because:

- it had not seen any clinical-effectiveness evidence comparing padeliporfin with the relevant comparators (see section 3.9)
- people who currently have the relevant comparators (radical therapies) are unlikely to have low-risk disease (the only population specified in the marketing authorisation for padeliporfin, see section 2).

Other factors

The recommendations apply to all people with prostate cancer

3.13 The committee noted that, as with previous appraisals of technologies for treating prostate cancer, its recommendations should apply to everyone with prostate cancer (that is, both trans-gender people and people with a prostate who do not identify as being male).

Padeliporfin is a new method of applying focal therapy

3.14 The committee heard differing views about whether padeliporfin was innovative in its potential to have a substantial effect on health-related benefits in low-risk disease. One clinical expert explained that adverse events resulting in sexual dysfunction do not capture important toxicities associated with prostatectomy such as loss of penile function and incontinence during sexual intercourse. These specific toxicities may be minimised with padeliporfin, but the company did not provide any supporting clinical evidence. The committee agreed that padeliporfin used a new method of applying focal therapy, but in the absence of data on clinical effectiveness compared with radical therapies, could not consider it a step change in treatment.

4 Review of guidance

4.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
October 2018

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sharlene Ting
Technical Lead

Jasdeep Hayre and Ross Dent
Technical Advisers

Jeremy Powell
Project Manager

ISBN: [to be added at publication]