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Jeremy Powell
NICE
By Email

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Dear Jeremy,

Thank you for the opportunity to contribute to this TA. I have forwarded to NICE the necessary paperwork including our comment form. I have a number of other points I would also wish to bring to the attention of the committee. These, together, represent a commissioning view of this. The comments don't quite "fit" into the headings within the comment form, therefore I have put them below.

Can you bring these to the attention of the committee when it meets. I hope to be there, and will gladly talk the committee trough them.

Preamble
Prostate cancer is the most common cancer in men in the UK and accounted for 10,168 deaths in 2008. Most deaths from prostate cancer are attributed to metastatic castration resistant prostate cancer (mCRPC). It seems unlikely that the use of this medicine will be uncommon.

Therefore a commissioner would expect its introduction to be based on very sound clinical evidence and a good case for cost effectiveness and affordability.

We have not undertaken a detailed review of the clinical evidence, as we are of the opinion that NICE will conduct a more capable review that we would be able to. We are aware of the CSAS evidence review and may use that at various points in the process.

This short paper focuses on some of the pertinent commissioning issues and does not cover in much detail at all the clinical evidence.

Key considerations for PCTs

There are few treatment options for men who have mCRPC that have progressed post docetaxel-based treatment and the prognosis for these patients is poor.

Mitoxantrone plus prednisolone (used off-license; administered intravenously) has come to be accepted as the standard care for this group of patients.

Best supportive care is always an option that needs to be considered within the care pathway, it may not be considered within the “active treatment” care pathway. However it IS a critical part of the WHOLE care pathway from a commissioner perspective.

In the pivotal trial (placebo controlled) there was a 3.9 month overall survival advantage. This needs to be weighted against the inappropriate comparator, whether the 3.9months is cost effective taking into account all the relevant costs and outcomes, and the broader impact of affordability on other aspects of prostate cancer prevention, treatment and palliation; and then broader cancer pathways.

Notwithstanding the fact we have stated we will not cover our interpretation of the key clinical effectivness evidence here, we would expect an indirect comparison is likely to be required to assess the effectiveness of abiraterone against the specified comparator mitoxantrone, alone or in combination with prednisolone, or best supportive care. Our view is that the available evidence to date has NOT considered the effectivness of this drug against the current standard of care NOR has it been compared against BSC – **as defined in the STA Scoping document**. This latter point is important when one considers the study published in NEJM in 2010 highlighting longer survival of Lung Cancer patients who received gold standard BSC compared to active treatment.

NHSBA will seek to review current epidemiology and clinical practice in this area to help PCTs better approximate the number of men who are currently receiving docetaxel and what proportion experience disease progression.

It is clear there are a wide range of treatments available for prostate cancer at various stages of the pathway. Our understanding is that patients with advanced prostate cancer might also be offered further corticosteroids, such as dexamethasone; radiotherapy; radiopharmaceuticals; analgesics; bisphosphonates; treatment with radioactive strotium-89 and further hormonal therapies. Best supportive care (no chemotherapy intervention) should also be discussed with men with obstructive uropathy secondary to CRPC and remains an active choice for some.

Mitoxantrone plus prednisolone is widely used in the UK for mCRPC patients who are fit for chemotherapy, even though it is not licensed for this indication, and has become the accepted standard care for this group of patients (1). Obviously abiraterone in this indication needs to stack up evidentially, economically and financially against this currently accepted standard of care.

From a commissioner perspective, abiraterone is obviously a competitor for funding with each of the above treatments and all other treatments – increased spend on one treatment is inevitably at the expense of something else. NHSBA is, for example, currently commencing discussions with one of our providers with respect to robotically assisted surgery – it might be that NHSBA views it is unable to fund both that and this new

medicine and therefore would need to have discussions with our surgeons and medical oncologists about preferences and opportunity cost.

NHSBA is aware that an alternative indication, “abiraterone for the treatment of chemotherapy naïve metastatic castration-resistant prostate cancer” is also due to be assessed using the STA process. If approved this would increase the number of patients eligible for abiraterone, and sharpen the issues I refer to above.

Epidemiology – impact on cost, expectations re population impact and affordability
The majority of men with advanced stage prostate cancer initially respond to hormonal therapy, however, the disease will eventually become resistant to standard hormonal therapy rendering it ineffective. This is known as hormone refractory prostate cancer or castrate resistant prostate cancer (CRPC), and is often metastatic (mCRPC).[1]

Prostate cancer is the most common cancer in men in the UK. In 2008, 37,051 men were diagnosed accounting for 24% of all new male cancers. Prostate cancer incidence is strongly related to age increasing from 155 cases per 100,000 men aged 55-59 years to 751 per 100,000 men aged 75-79 years. It is estimated that the lifetime risk of being diagnosed with prostate cancer is 1 in 9 men in the UK.[4]

Around 80% of men have histological evidence of cancer of the prostate by age 80 years, but only 3.8% will die from the disease. Prostate cancer accounted for 10,168 deaths in the UK in 2008, around 12% of all male deaths from cancer, and is the second most common cause of cancer death in men after lung cancer. Mortality is strongly related to age with 93% of deaths occurring in men over 65 years.[4] Most deaths from prostate cancer are attributed to mCRPC.[2,5]

Hormonal therapies are initially effective in 80% of men with metastatic prostate cancer, but after around 18 months the disease usually becomes unresponsive to hormone treatment and will progress.[2] The prognosis for patients with mCRPC is poor, with survival not expected to exceed 9 to 12 months.[2]

Cancer Research UK indicates that 20% to 30% of men have metastatic prostate cancer at first diagnosis.[4] This is in agreement with the figure used by NICE in the costing template for docetaxel of 22%.[6] This also estimated an additional 17% of previously diagnosed cancers would progress to this stage each year. This costing template assumes that 100% of all metastatic prostate cancer cases would become refractory to first line hormone therapy and that 45% would subsequently be put on docetaxel based treatment. The remaining 55% would receive mitoxantrone plus prednisolone (15%) or prednisolone alone (40%). These estimates were produced before docetaxel had been widely adopted by the NHS and so it is not clear whether these prospective estimates are accurate. The costing report did not estimate the proportion of mCRPC patients that might become resistant to docetaxel-based treatment, or the proportion of patients that would have died before receiving treatment.

A review of current practice may help PCTs better approximate the number of men who are currently receiving docetaxel; what proportion experience disease progression during treatment, and consequently, the number of potential candidates for treatment with abiraterone for this indication.

Economic model

The incremental costs might well be substantial – increasingly commissioners will have expectation that the introduction of new technologies in the context of a flat or decreasing budget scenario will be met by disinvestments elsewhere in the same pathway area

It is difficult to estimate the financial impact of a positive recommendation for abiraterone as the cost of the drug is unknown in the UK. The relevant population for local activity will be men with mCRPC whose disease has progressed on or after docetaxel-based chemotherapy.

An estimate of potential treatment need can be derived from the NICE costing template on implementing docetaxel for treatment of mCRPC (5). This prospectively estimated the proportion of men with mCRPC that would be prescribed docetaxel once it was adopted by the NHS. It is not known how closely these projected estimates of treatment match actual clinical practice. We applied the NICE costing template proportions to the prostate cancer incidence figures for the UK in 2008.

This indicated that there would be approximately 14,450 cases of metastatic disease in the UK in 2008. All of whom would eventually become refractory to first line hormone therapy, and 45% of whom would subsequently receive docetaxel treatment for mCRPC (6,503 patients) (Table 2). However, it is not clear how many of these patients would experience disease progression during or after docetaxel treatment and subsequently be indicated for abiraterone.

Table 1: Estimated number and proportion of cases of metastatic prostate cancer, adapted from NICE TA101 costing template.

NB: Figures may not sum exactly to totals due to rounding

Description	Proportion (%)	Number
Annual incidence of prostate cancer	100	37,051
New cases that are metastatic at diagnosis	22	8,151
Metastatic due to progression of existing disease	17	6,299
Total annual metastatic disease	39	14,450
Metastatic disease refractory to first line hormone therapy	100	14,450
Metastatic disease receiving docetaxel plus prednisolone	45	6,503
Metastatic disease receiving prednisolone	40	5,780
Metastatic disease receiving mitoxantrone plus prednisolone	15	2,168

These estimates do not factor in the proportion of patients who die before; during or after each treatment step and so should be treated with caution and act only as broad estimates.

Using the European Age-Standardised Incidence Rate of 97.9 per 100,000 male population in the UK from Cancer Research UK[4] and the NICE TA101 costing template estimates of treatment proportions,(5) we estimate that approximately 17 patients per 100,000 male population will be treated with docetaxel plus prednisolone, and therefore could be eligible for treatment with abiraterone.

A review of current practice may help PCTs better approximate the number of men who are currently receiving docetaxel and what proportion experience disease progression.

A “worst case” estimate of the potential cost of this drug suggests that it might, as a rough guide, cost £425,000 per 100,000 men (based on US pricing – estimated £25k per patient. This is based on the U.S.A quoted cost, recent exchange rates, and that the drug is used in all men who had previously received docetaxel plus prednisolone.) There are approximately 270,000 men in Bradford and Airedale.

It is obviously difficult to accurately estimate the burden of mCRPC in the population as epidemiological data is sparse. Reliable estimates of the number of individuals with mCRPC that have progressed post docetaxel-based treatment are unavailable. As a guide we estimate that about 17 per 100,000 men (about 8.5 per 100,000 population) would be eligible for abiraterone for the indication currently under assessment. This would equate to an approximate cost of £212,500 per 100,000 population (plus any associated activity). For NHSBA Approx £1.1m.

In epidemiological terms, taking into account response rates, OS advantage and those that do gain benefit AND those that don’t, this investment would allow 17 men to have a chance of extending life by two to four months above current or no treatment respectively.

NHSBA currently (09 / 10 Programme Budget Data) spends £51m on cancer. Thus a spend of £1.1m on medicine equates to almost 2.5% of the cancer budget spend on one medicine. For this level of expenditure, it seems reasonable to expect this medicine to have a significant effect on survival, life expectancy and possibly mortality rate for prostate cancer. Particularly given the inherent opportunity cost of other treatments forgone.

Ethical issues

There are few treatment options for men who have mCRPC that have progressed post docetaxel-based treatment. The prognosis for these patients is poor. Mitoxantrone plus prednisolone (used off-license) has come to be accepted as the standard care for this group of patients. It should be clear that BSC is always an option.

NICE has a policy for valuing drugs that extend life in people who have a short life-expectancy. This policy is applicable for treatments that have been through an appraisal by NICE and where the ICER exceeds the upper threshold of the range normally considered to represent a cost-effective use of NHS resources in comparison to other funded therapies by the Appraisals Committee (£30,000).

The policy is applied if in addition to the estimated QALY threshold over £30,000 all of the following criteria apply:

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
3. The treatment is licensed or otherwise indicated, for small patient populations.

A median survival of just 10.9 months in the placebo group suggests the drug may be eligible for consideration. An indirect comparison against the existing standard of care will

need to be made to fully meet requirement two, as no study has compared abiraterone with current NHS treatment directly.
The size of the population it is licensed or otherwise indicated for is uncertain, especially in light of the second appraisal underway in chemotherapy naive patients.

It is possible that the treatment will be appraised in accordance with NICE's policy for treatments that extend life in patients with a short life-expectancy. However, overall survival with abiraterone will need to be modelled against current standard care. Furthermore, accurate assessment of the eligible population for all indications will be needed

As I said above, I would be more than happy to talk the committee through short paper.

Yours sincerely

[redacted]
NHS Bradford and Airedale

Short references

1. National Institute for Health and Clinical Excellence. (2008) Prostate cancer: diagnosis and treatment. CG58. London: National Institute for Health and Clinical Excellence. Available at: http://www.nice.org.uk/cg58 [access date 09/09/11].
2. National Institute for Health and Clinical Excellence. (2006) TA101. Prostate cancer (hormone-refractory) docetaxel. TA101. London: National Institute for Health and Clinical Excellence. Available at: http://guidance.nice.org.uk/TA101 [access date 09/09/11].
4. Cancer Research UK. (2008) Prostate Cancer Statistics. London: Cancer Research UK. Available at: http://info.cancerresearchuk.org/cancerstats/types/prostate/ [access date 09/09/11].
5. National Institute for Health and Clinical Excellence. (2006) TA101. Prostate cancer (hormone-refractory) docetaxel. TA101. London: National Institute for Health and Clinical Excellence. Available at: http://guidance.nice.org.uk/TA101 [access date 09/09/11]