National Institute for Health and Clinical Excellence

Single (STA)

Dutasteride for reducing the risk of developing prostate cancer

Response to consultee and commentator comments on the final remit and draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	National Collaborating Centre for Cancer	No comment.	Comment noted, no action required.
	Commissioning Support Appraisals Service	Cancer Research UK report that in England and Wales there were 32,679 new cases of prostate cancer diagnosed in 2007, and 9,150 deaths from prostate cancer in 2008. They also report that about 75% of cases occur in men aged 65 and over. Other than this the background information appears to be accurate.	Comment, noted. The background section has been amended accordingly.
	GlaxoSmithKline	The background information is appropriate however the current evidence linking increased body mass index and prostate cancer is not strong.	Comment noted. The background section has been amended accordingly.
The technology/ intervention	National Collaborating Centre for Cancer	Yes.	Comment noted, no action required.
	Commissioning Support Appraisals Service	The information about dutasteride appears accurate.	Comment noted, no action required.
	GlaxoSmithKline	The description of the technology is appropriate.	Comment noted, no action required.

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Population	National Collaborating Centre for Cancer	Yes it is appropriately defined. There are no other groups that should be considered.	Comment noted, no action required.
	Commissioning Support Appraisals Service	The population definition is broad, which seems appropriate given that there may not be an accepted definition for men at "high risk" of prostate cancer. It may be appropriate to consider trials separately based on the definition of "high risk" used or based on the level of baseline risk (based on control group rates of prostate cancer).	Comment noted, no action required.
	GlaxoSmithKline		Comment noted, no action required. Comment noted. The scope has been amended accordingly. Comment noted, no action required.
Comparators	National Collaborating Centre for Cancer	Yes.	Comment noted, no action required.
	Commissioning Support Appraisals	The "no intervention" comparator appears appropriate as there are no standard treatments available for reducing the risk of prostate cancer in men at high risk.	Comment noted, no action required.

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	GlaxoSmithKline	There is currently no other licensed or frequently prescribed chemoprevention for prostate cancer. The current management for men identified as being at increased risk of prostate cancer is by repeat PSAs, digital rectal examinations (DREs), biopsies and radiological investigations as deemed appropriate by the patients' Urologist. This can be described as current standard of care.	Comment noted.
Outcomes	National Collaborating Centre for Cancer	Re-biopsy rate and the need for radical treatment should be added.	Comment noted. The scope has been amended accordingly.
	Commissioning Support Appraisals Service	The outcomes are appropriate, though risk of developing prostate cancer could be considered as a separate outcome. Dutasteride is known to reduce PSA levels in the blood, therefore this should be taken into account for when considering trials using PSA as a proxy for assessing the presence of prostate cancer.	Comment noted, no action required.
	GlaxoSmithKline	The listed outcomes are all important for assessing the benefits of a chemoprevention for prostate cancer. Severity of prostate cancer is defined by Gleason grade and tumour staging. The REDUCE trial has been analysed in terms of low and high grade tumours determined from Gleason grades and these low and high grade tumour categories have been incorporated into the cost-effectiveness analyses. In addition to analysing PSA levels, PSA utility (sensitivity and specificity measurement) for detecting clinically relevant prostate cancer is also an important outcome measure for this disease. Two other important outcomes are high grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) which are considered probable precursor lesions of prostate cancer. The incidence of both of these outcomes was measured in the REDUCE study. The estimation of mortality caused by low grade prostate cancer is dependent upon the current therapeutic strategies employed to treat these cancers.	Comment noted. High grade prostatic intraepithelial neoplasia and atypical small acinar proliferation have been included in the outcomes list. Comment noted, no action required.

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		Estimates of reductions in mortality produced by the reduction of low grade prostate cancers with dutasteride are therefore difficult to make. Low grade Gleason cancers are currently managed with radical therapy or active surveillance with signs of progression triggering radical therapy. These therapeutic strategies are associated with significant costs and morbidity. As dutasteride is not a chemotherapeutic agent, the benefits resulting from chemoprevention are more appropriately measured against the treatment strategies employed to manage the cancers that are prevented. Summaries of the mortality data for low grade prostate cancer will be provided but these will not be incorporated into the model.	
Economic analysis	National Collaborating Centre for Cancer	No comment.	Comment noted, no action required.
	Commissioning Support Appraisals Service	If treatment needs to continue for a lifetime this would be an appropriate time horizon for the economic analysis. Long term data on the effects of dutasteride on prostate cancer risk, mortality, and other outcomes may not be available from RCTs. Screening costs, costs of diagnostic investigations such as biopsies and treatments such as prostatectomy and radiotherapy should be included in the analysis. Quality of life impacts of these investigations and treatments should also be considered.	Comment noted, no action required.
	GlaxoSmithKline	A decision-analytic Markov model will be used to assess the cost-effectiveness of dutasteride on reducing the risk of prostate cancer. The cost-effectiveness analysis will be expressed in terms of incremental cost per quality-adjusted life year. The relevant time horizon for the cost-effectiveness model will range from 4 years (REDUCE study duration) up to lifetime. The base case model horizon will be in line with how we believe dutasteride will be incorporated into clinical practice.	Comment noted, no action required. Comment noted. The NICE methods guide states “A lifetime horizon should normally be adopted if a treatment affects survival at

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			a differential rate when compared with the relevant comparator".
		Dutasteride therapy requires no additional follow up. It is not expected that dutasteride will require additional PSA testing compared to current UK clinical practice. Individuals at increased risk of developing prostate cancer will typically be followed up using a combination of DRE, PSA testing and TRUS biopsy.	Comment noted, no action required.
		Men at increased risk of prostate cancer will be identified in concordance with the current Department of Health's Prostate Cancer Risk Management Programme (PCRMP) guidelines as determined by age-adjusted PSA values. Dutasteride therapy will therefore not lead to additional case finding compared to current UK clinical practice.	Comment noted, no action required.
Equality and Diversity	National Collaborating Centre for Cancer	No comment.	Comment noted, no action required.
	Commissioning Support Appraisals Service	As men of black African or black Caribbean origin are at increased risk of prostate cancer, the effects of dutasteride in this group should be considered in the review.	Comment noted, no action required.
	GlaxoSmithKline	Black African/black Caribbean men have a higher risk of developing prostate cancer. Although they would be likely to disproportionately benefit from dutasteride use, there were insufficient patients of black African/black Caribbean ethnicity recruited into the REDUCE trial to enable a robust assessment of the effects of dutasteride on this sub-population of men,	Comment noted, no action required.

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		therefore this sub-population will not be addressed separately. Inequalities relating to the management of men's health currently exist. This is partially due to the reluctance of men to seek medical advice coupled with men's health being low on the healthcare agenda as evidenced by the fact that male LUTS does not feature on the Quality Outcomes Framework despite 1.2million men being symptomatic and nearly 700,000 untreated. Between 2001-2006 there were on average 34,298 cases of breast cancer and 27,740 cases of prostate cancer diagnosed in England with the 2007 five year relative mortality rates for these two cancers being 18.0% and 23.0% respectively. Thus, mortality is higher for prostate cancer than it is with breast cancer. Female cancers have been targeted through the breast cancer screening programme and the introduction of a vaccination programme for the prophylaxis of cervical cancer. There have been no targeted interventions aimed at male cancers.	
Other considerations	GlaxoSmithKline	Subgroup efficacy analyses will be presented based on age, PSA level at baseline, BMI, prostate volume, family history of prostate cancer, and a combination of age and family history. It is proposed that the target population for the UK will be identified as men with a family history of prostate cancer and elevated PSA levels, adjusted for age, in order to target a high risk population which is consistent with the current PCRMP guidelines for referral for suspected prostate cancer. This population will be examined in the cost-effectiveness model, along with the total REDUCE population.	Comment noted. If the evidence allows subgroups based on the level of risk at which intervention with dutasteride is clinically and cost-effective will be considered. Risk factors may include age, PSA level, body mass index, family history and ethnicity (men of black African or black Caribbean). Comment noted, no action required.

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Questions for consultation	National Collaborating Centre for Cancer	1) Yes it is innovative. 2)No. 3)The results of the REDUCE trial.	Comment noted, no action required.
	Commissioning Support Appraisals Service	Subgroup analysis according to categories of risk would be appropriate as the "high risk" population definition is currently broad, e.g. age, family history, ethnicity, PSA level. A Cochrane review has suggested that the 5-alpha reductase inhibitors such as dutasteride may be less effective in men with PSA levels above 4ng/ml at baseline; therefore it may be appropriate to assess men with levels below and above this level separately.	Comment noted. If the evidence allows subgroups based on the level of risk at which intervention with dutasteride is clinically- and cost-effective will be considered. Risk factors may include age, PSA level, body mass index, family history and ethnicity (men of black African or black Caribbean).
	GlaxoSmithKline	Clinical guidelines CG58 recommend that patients with low risk prostate cancer are offered active surveillance which requires regular PSA monitoring and TRUS biopsies to monitor tumour progression. For men in watchful waiting, approximately 30% progress to require radical treatment. Men who are diagnosed with low Gleason grade prostate cancers thus face a difficult decision with regards to treatment with approximately 60% of men currently opting for primary radical therapy. Dutasteride provides an opportunity for a "step-change" in patient care by reducing the risk of low risk prostate cancers developing and so reducing the requirements for radical therapies which can lead to substantial side effects and a negative impact on patients' quality of life. Evidence from the REDUCE trial indicates that PSA sensitivity and specificity is improved with dutasteride. This benefit is currently difficult to incorporate into the QALY calculation but it is an important benefit of dutasteride. A publication on the effects of dutasteride on improving PSA utility is due to be published in the Journal of Urology in January 2011. This and all results from additional analyses of PSA utility conducted on the REDUCE data will be	Comment noted, no action required.

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		discussed in the appraisal submission. Other benefits of dutasteride that we believe are relevant to this appraisal are the benefits experienced by men in the target population who have concurrent BPH. GSK believes that the symptom improvement and reduction in risk of acute urinary retention and BPH-related surgery in these men treated with dutasteride should be taken into consideration.	Comment noted.
Additional comments on the draft scope.	National Collaborating Centre for Cancer	What criteria are used in UK clinical practice to identify men who are at increased risk of developing prostate cancer? How are risk factors such as age and ethnicity taken into consideration in the assessment of increased risk? Men with a strong family history are likely to undergo more frequent PSA testing but the other factors listed are not used uniformly to identify men at increased risk. Have the most appropriate comparators for the prevention of prostate cancer been included in the scope? There is evidence on the use of finasteride for prostate cancer prevention but this is not within its licensed indication. What do you consider to be the relevant clinical outcomes and other potential	Comment noted, no action required. Comment noted. It was discussed at the scoping workshop that finasteride had no license in the reduction of risk prostate cancer. It was noted that EMA has warned about the apparent hazards of finasteride. Therefore finasteride was not considered to be an appropriate comparator .

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		health related benefits of dutasteride in the prevention of prostate cancer, particularly when compared with currently used treatment options? How should severity be defined? The key outcome with dutasteride is a reduction of the risk of overtreatment of prostate cancer without any adverse impact on prostate cancer mortality.	Comment noted, no action required. Comment noted, no action required.
	National Collaborating Centre for Cancer	Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? No comment. Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality? None I am aware of.	Comment noted, no action required. Comment noted, no action required.
	Commissioning Support Appraisals	Although the existing RCT of dutasteride treatment in men at high risk of prostate cancer suggests that risk of prostate cancer is reduced, it is not clear whether this is due to shrinking pre-existing small prostate cancers that would not have become clinically evident. Considering this it may be best to wait	Comment noted. This issue arises in many technology appraisals. This will not affect the appraisal of this

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	Service	until longer term data on the effects of dutasteride prophylaxis on prostate cancer mortality are available.	technology.
	Royal College of Physicians on behalf of National Cancer Research Institute Royal College of Physicians Royal College of Radiologists Association of Cancer Physicians Joint Collegiate Council for Oncology	The major comments received from our experts are that this is a very promising area, but maybe one where a NICE appraisal is premature. There are no data on the effects of dutasteride on reducing mortality from prostate cancer, and long term this would be the key indicator of efficacy. As an intermediate endpoint, reducing prostate cancer incidence (even that of high grade disease) is flawed, as we simply do not know how this might translate into mortality reductions.	Comments noted. This issue arises in many technology appraisals. This will not affect the appraisal of this technology.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

- British Uro-Oncology Group
- Department of Health
- NHS Quality Improvement Scotland
- Medicines and Healthcare Products Regulatory Agency
- Research Institute of the Care of Older People
- Royal College of Nursing
- Royal College of Pathologists
- United Kingdom Oncology Nursing Society
- Welsh Assembly Government