Aberdeen HTA Group

Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer

Erratum to the ERG report

Completed 30 April 2018

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Contains CIC/AIC

This document is intended to replace pages 2, 5, 6, 25, 38, 46, 50, 65, 81, 102, 109 and 124 of the original ERG assessment report for *Abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer*, which contained a few inaccuracies. The amended pages follow in order of page number below.

newly diagnosed high risk mHSPC in combination with ADT and that the terms mHNPC and newly diagnosed mHSPC are effectively the same because newly diagnosed patients are, by default, hormone naïve. The company did not consider orchidectomy and bicalutamide monotherapy as clinical experts advised that these are seldom used in the UK. The comparators presented in the company submission are ADT alone (including LHRH agonist therapy) and docetaxel (DOC) plus ADT. The company state that clinical experts provided validation that there is no difference in the type of ADT, thus justifying their approach. The company submission includes all the outcomes listed in the NICE scope and reports additional outcomes from the LATITUDE trial: progression free survival following subsequent therapy, time to symptomatic local progression, prostate cancer-specific survival, time to chronic opiate use, castration status.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence submitted by the company consist of one RCT, the LATITUDE trial (1199 participants), with supporting evidence of one further RCT, the STAMPEDE trial (1917 participants). LATITUDE is a manufacturer-sponsored, multinational, randomised, double-blind, placebo-controlled Phase III trial that investigated abiraterone acetate with prednisone/prednisolone (AAP) plus ADT (597 participants) versus ADT plus placebo (602 participants). The company consider the ADT plus placebo arm equivalent to ADT alone. The company also maintain that LATITUDE is the only RCT providing data specific to the target population of people with newly diagnosed, high-risk mHSPC. The investigator-sponsored STAMPEDE trial represents the largest evidence base of AAP plus ADT in early prostate cancer data relevant to UK practice but include a broader patient population than LATITUDE, and does not report data separately for high risk disease/high volume patients.

The co-primary outcomes assessed in the LATITIDE trial were overall survival (OS) and radiographic progression free survival (rPFS). OS was also the primary outcome in STAMPEDE whilst failure free survival (FFS) was the intermediate primary outcome. In the LATITUDE trial, treatment with AAP plus ADT was associated with a 38% reduction in the risk of death compared with ADT alone (HR=0.62 [95%CI: 0.51–0.76]; p<0.001). The overall survival rate at three years was 66% in the AAP +

The Functional Assessment Cancer Therapy-Prostate (FACT-P) and Brief Pain Inventory (BPI) quality of life measures, looked at differences of change from baseline for both AAP+ADT and DOC+ADT treatment groups over four time points 3, 6, 9 and 12 months in LATITUDE (ITT) and CHAARTED (high volume disease - HVD). Sub-group analyses were conducted by the company whereby high risk disease (HRD) and HVD patients in LATITUDE were selected post-hoc. At 3 months, there was a 99.7% probability that AAP+ADT was associated with better quality of life than DOC+ADT (95% CrL 1.18-7.19). AAP estimates improved further over time as did the DOC estimates (not to the same extent and never to the level of AAP), and the probability of AAP+ADT being superior remained high at 6, 9 and 12 months (94.5%, 97.0% and 92.3%, respectively). BPI results showed an 88-100% probability of AAP+ADT being better at reducing pain than DOC+ADT over the 12-month period. Pain in the DOC group increased with time whereas with AAP they remained steady if not further reduced. The sensitivity analyses were comparable for FACT-P and BPI.

In the absence of any head-to head studies, further indirect comparisons were conducted for a group of men with disease progression (for the mCRPC group with respect to the effectiveness of AAP with other treatments including DOC). These were not presented in the clinical effectiveness section of the submission but only in the cost-effectiveness section. The company used the COU_AA_302 study, which directly compared abiratone plus prednisolone with placebo plus with prednisolone, and other studies which compared different treatments with placebo or best standard care. In particular, the company focused on DOC (the TAX327 study comparing DOC to a different placebo, mitoxantrone), radium-223 (the ALSYMPCA study with prednisolone as placebo) and enzalutamide (the PREVAIL study with prednisolone as placebo). In general, the estimates show that AAP is comparable with other treatments.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

LATITUDE has provided the only evidence so far of AAP+ADT compared with ADT alone for the treatment of men with mHSPC. The ERG agree with LATITUDE results suggesting that AAP+ADT to be beneficial for the primary outcomes of OS and rPFS and for most of the secondary outcomes of safety and quality of life compared to

ADT. In terms of safety, AAP+ADT had a slight increased risk for hypertension and hypokalaemia. The results of LATITUDE are similar to those of the STAMPEDE trial. However, the STAMPEDE patient group was broader and while the company have conducted similar analyses on a *post hoc* subgroup profiled to be similar to the LATITUDE population, they rightly have not combined the results of these studies. Overall, the results from the LATITUDE trial provide evidence of benefits of AAP+ADT over ADT alone for the treatment of patients with mHSPC for the outcomes survival, progression and quality of life. The risk of some safety outcomes increased for AAP but the ERG agree that these may be well treated medically.

With no head-to-head trials assessing the effects and safety of abiratone versus the only other relevant comparator, DOC, identified for the patient group of interest, mHSPC, indirect treatment comparisons (ITC) were a sensible option. The company used a Bayesian network meta-analysis (NMA). The primary outcomes were based on three RCTs: LATITUDE, which compared AAP+ADT to ADT alone, and CHAARTED and GETUG-ARG 15, both of which compared DOC in conjunction with ADT to ADT alone. The Bayesian ITC showed that, when compared to DOC+ADT, AAP+ADT was highly likely to be superior in terms of rPFS, and at least as effective, but likely superior, in terms of OS. However, there is uncertainty about the size of effect as reflected in the credible intervals. Consistent results were attained through sub-group analyses using many combinations of patient groups in attempt to mirror the LATITUDE population. The results did not vary drastically but it is not clear which might be the most reliable.

For the relapsing/progression patients, the mCRPC group, the ITC used were Bucher pairwise estimates comparing other treatments with AAP. This approach requires many independent steps and so, intuitively, seems less robust compared to the NMA above, but the ERG agree it was probably the only course of action to accommodate the lack of studies and comparison arms. Each study compared a treatment with a ‘placebo’ although not always the same one. The conclusion that AAP is comparable to other treatments with regard to OS and rPFS is probably reasonable. The ITC analyses for both the mHSPC and mCRPC patient groups, have basic assumption violations of contextual heterogeneity which the company discussed in some detail and acknowledge the subsequent limitations. However, no checks were provided for statistical heterogeneity or consistency. All of these mean that clinically,

<table>
<tr><td>List price and average cost of a course of treatment</td><td>The NHS list price of AA 500mg tablets x 56 = £2,735.00.

Treatment with AA is continued until disease progression. The median duration of treatment in men with newly diagnosed high-risk mHSPC is 24 months.[41]

<table><tr><td>Drug cost [list price]</td><td>£2,735 [28 days]</td></tr><tr><td>Packs per year</td><td>365/28 = 13</td></tr><tr><td>Drug cost per patient per year*</td><td>£35,652.68</td></tr></table>
*Maximum drug cost presented, assuming all patients who are initiated on abiraterone acetate stay on treatment for a full year.</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>Abiraterone acetate is available to NHS customers through a confidential Commercial Access Arrangement (CAA) with NHS England. This CAA will extend to cover the use of AAP + ADT in patients with newly diagnosed high-risk mHSPC.

[redacted]</td></tr>
<tr><td colspan="2">Key: AA, abiraterone acetate; CYP17, 17α-hydroxylase; DHEA, dehydroepiandrosterone; EPAR, European Public Assessment Report; LHRH, luteinising-hormone-releasing hormone; PAS, patient access scheme; SPC, summary of product characteristics.</td></tr>
</table>

3.2.1 Safety

Abiraterone acetate (AA) may cause hypertension, hypokalaemia, fluid retention and cardiac failure due to increased mineralocorticoid levels. Caution is required in treating patients whose underlying medical conditions might be compromised by these contraindications (e.g. cardiac glycosides, severe renal impairment, heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia).

This is the only trial providing data specific to the target (i.e., licensed) population of interest, and thus is the primary evidence source for the company submission. The investigator-sponsored STAMPEDE study[45] represents the largest evidence base of data specific to UK clinical practice for AAP + ADT in early prostate cancer but include a broader patient population than LATITUDE and does not report data separately for HRD/HVD patients. Due to these limitations, data from the STAMPEDE trial are referenced as supportive evidence only in the company submission.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Characteristics and critique of the trials included in the systematic review of clinical effectiveness

As stated previously in section 4.1.5, the main evidence for the company submission is taken from the LATITUDE trial[41] with supporting evidence presented from the STAMPEDE trial[45]. A summary description of these two trials is presented in Table 9.

Table 12 Summary of secondary endpoints for the LATITUDE intention to treat population (reproduced from Table 11, Document B of the company submission)

	AAP + ADT (n=597)	ADT alone (n=602)
Time to pain progression		
Events, n (%)	233 (39.0)	289 (48.0)
Median months (95% CI)	NR (36.5, NR)	16.6 (11.1, 24.0)
HR (95% CI) [p-value]	0.70 (0.58–0.83) [<0.001]	
Time to subsequent prostate cancer therapy		
Events, n (%)	191 (32.0)	322 (53.5)
Median months (95% CI)	NR ([redacted])	21.6 ([redacted])
HR (95% CI) [p-value]	0.42 (0.35–0.50) [<0.001]	
Time to life-extending subsequent therapy for prostate cancer		
Events, n (%)	125 (20.9)	246 (40.9)
Median months (95% CI)	[redacted]	[redacted]
HR (95% CI) [p-value]	[redacted]	
Time to initiation of chemotherapy		
Events, n (%)	109 (18.3)	191 (31.7)
Median months (95% CI)	NR ([redacted])	38.9 ([redacted])
HR (95% CI) [p-value]	0.44 (0.35–0.56) [<0.001]	
Time to PSA progression		
Events, n (%)	241 (40.4)	434 (72.1)
Median months (95% CI)	33.2 (27.6, NR)	7.4 (7.2, 9.2)
HR (95% CI) [p-value]	0.30 (0.26–0.35) [<0.001]	
Time to next SRE		
Events, n (%)	[redacted]	[redacted]
Median months (95% CI)	NR (NR, NR)	NR (NR, NR)
HR (95% CI) [p-value]	0.70 (0.54–0.92) [0.009]	

Key: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not reached; PSA, prostate specific antigen; SRE, skeletal-related event.
Source: Fizazi et al. 2017[41] LATITUDE CSR, 2017 European Public Assessment Report[37].

In the LATITUDE trial, treatment with AAP+ADT significantly reduced the time to subsequent therapy for prostate cancer. The median time to subsequent therapy was not reached in the AAP + ADT group, it was 21.6 months for the ADT group (HR=0.415 [95%CI: 0.346–0.497], p<0.0001). Twice as many ADT alone patients required life-extending subsequent therapy (either docetaxel, enzalutamide, cabazitaxel, radium-233 or AAP) compared with those who received AAP+ADT (40.9% versus 20.9% respectively). The median time to life-extending subsequent therapy was not reached in the AAP + ADT group and was 29.5 months in the ADT

abiraterone in mHSPC, these data should only be considered as strong supporting evidence of AAP's clinical effectiveness, with the direct evidence from LATITUDE being the most appropriate source to inform the economic modelling in the licensed population.

Table 13 Meta-analyses of AAP+ADT versus ADT alone for the outcomes overall survival and disease progression (reproduced from Table 16, Document B of the company submission)

OS			
	Direct Evidence: AAP+ADT vs. ADT	**Direct Evidence: AAP+ADT vs. ADT**	**Meta-Analysis: AAP+ADT vs. ADT**
Trial Name	LATITUDE	STAMPEDE	Rydzewska et al. 2017[48]
Population	ITT	M1	
HR [95% CrI]	0.62 [0.51, 0.76]	0.61 [0.49, 0.75]	0.62 [0.53, 0.71]
Disease progression (i.e. rPFS or PFS)[a]			
	Direct Evidence: AAP+ADT vs. ADT	**Direct Evidence: AAP+ADT vs. ADT**	**Meta-Analysis: AAP+ADT vs. ADT**
Trial Name	LATITUDE	STAMPEDE	Rydzewska et al. 2017[48]
Population	ITT	M1	
HR [95% CrI]	0.47 [0.39, 0.55]	0.43 [0.36, 0.52]	0.45 [0.40, 0.51]
Key: AAP, abiraterone acetate prednisone/prednisolone; ADT, androgen deprivation therapy; CI, confidence interval; CrI, credible interval; HR, hazard ratio; ITT, intent to treat; M1, metastatic; OS, overall survival; rPFS, radiographic progression-free survival. **Notes:** [a], PFS=radiological or clinical progression-free survival			

Adverse reactions

Treatment exposure

The median treatment duration in the safety population of the LATITUDE trial was 24 months in the AAP + ADT arm and 14 months in the ADT alone arm.[41]

[redacted] A total of 91.8% of patients in the AAP + ADT group and 86.0% of patients in the ADT alone group received ≥6 cycles of study drug; 54.5% and 29.7% of patients, respectively, received ≥24 cycles.

Dose reductions were reported for [redacted]% of patients treated with AAP + ADT and [redacted]% of patients treated with ADT alone, while dose interruptions were reported for

Statistical comparison of AAP versus docetaxel (DOC) for the primary outcomes OS and rPFS was only possible using ITC methods. The patient populations of two RTCs, CHAARTED (790 participants) and GETUG-AFU 15 (385 participants), which compared DOC +ADT with ADT alone using post-hoc selected sub-groups of newly diagnosed patients with high volume disease (HVD), were considered to be comparable with those in LATITUDE. The company used Bayesian network meta-analyses with fixed effects to find the indirect results of AAP+ADT versus DOC+ADT. The results presented in Table 21 demonstrate that, when compared with DOC+ADT, AAP+ADT has a 71.8% probability of being the better life prolonging treatment option (HR 0.92, 95% CrL 0.69-1.23) and a 92.9% probability of being better at delaying disease progression (HR 0.76, 95% CrL 0.53-1.10). Various sensitivity analyses examined the effect of post-hoc selection of the HVD patients rather than the high risk disease (HRD) group of LATITUDE; the inclusion of the M1 group from STAMPEDE (for both AAP+ADT and DOC+ADT) and the inclusion of those treated prior to current treatment or not. The results of the sensitivity analyses varied but there was a consistent trend in favour of AAP+ADT.

Results of sensitivity analyses of time to skeletal-related events (SRE) were similar in the indirect comparison between AAP+ADT and DOC+ADT, [redacted] but with a Bayesian pairwise probability of [redacted].

Only two RCTs, LATITUDE (AAP+ADT versus ADT) and GETUG-AFU 15 (DOC+ADT versus ADT, presumably newly diagnosed HVD patients) could be included into an ITC for the assessment of secondary outcome measures of safety. No sensitivity analyses were reported. When the AAP+ADT group (n=597) was indirectly compared to the DOC+ADT group (n=189), [redacted]

However, AAP+ADT was found [redacted]

significantly lower at 3 months (-3.09, p=0.02) but significantly higher at 12 months compared to ADT (+2.85, p=0.04). But differences did not exceed the minimum clinically meaningful change at any time point, which was taken to be a change of 6 to 10 points. Both arms reported significantly poorer FACT-Taxane scores compered to baseline. Brief pain inventory scores were similar between the arms. The authors conclude that "*Although ADT+D was associated with statistically worse QOL at 3months, QOL was better at 12months for ADT+D patients than for ADT patients. Both arms reported a similar minimally changed QOL over time, suggesting that ADT+D is not associated with a greater long-term negative impact on QOL*".

[redacted]The company do not reference minimum clinically meaningful changes and conclude that "*Results of the ITC showed treatment with AAP+ADT was associated with notable benefits in HRQL compared to DOC+ADT. These benefits were observed from three months and sustained for at least one year after treatment*".

A crude reading of the company ITC and the results of Morgans et al[54] suggests that the 12 month FACT-P improvement from AAP+ADT compared to ADT is roughly double that of the improvement from DOC+ADT compared to ADT.

The model requires estimates for quality of life increments or decrements relative to ADT for patients in rPFS. For rPFS specific estimates of FACT-P changes there may be some confounding between both AAP+ADT and ADT and DOC+ADT and ADT in the RCT data due to more progression with ADT than with either AAP+ADT or DOC+ADT.

However, given the greater rPFS superiority for AAP+ADT over ADT compared to DOC+ADT over ADT, any such confounding might be expected to benefit AAP+ADT more than DOC+ADT. Yet, it cannot be unambiguously stated that the literature concludes that FACT-P changes for those remaining in rPFS are better among AAP+ADT patients than among ADT (post DOC+ADT) patients, or that they are better among ADT (post DOC+ADT) patients than among ADT patients.

Table 40 Unplanned medical resource use: mHSPC

	Unit cost	AAP+ADT	ADT
Radiotherapy procedure	£101	[redacted]	
Radiotherapy preperation	£288		
MRI	£180		
CT scan	£120		
X-ray	£171		
Hospitalisation	£307		
Oncologist	£173		
Urologist	£103		
Surgery	£12,778		
Emergency room	£148		
General practitioner	£38		
Annual cost		£1,192	£1,513

This is augmented with the adverse event frequencies taken from the LATITUDE trial for AAP+ADT and ADT, and from Gravis et al[58] for DOC+ADT which result in additional annual costs of around £630, £580 and £1,105 respectively. The higher cost for DOC+ADT is due to 32% having neutropenia, which may be reasonable to apply to those receiving docetaxel but may be less reasonable to those who have completed their course of docetaxel, i.e., ADT (post DOC+ADT) patients, which is why the model applies the AE rates related to ADT during the off-treatment period following completion of treatment with docetaxel.

mCRPC drug and administration costs

The 1st line mCRPC compliance ratios for abiraterone and enzalutamide are assumed to be 100%[1]. This seems appropriate due to the curves that they are applied to being labelled discontinuation curves. However, for docetaxel, cabazitaxel and radium-223 the company uses treatment completion rates to estimate compliance rates of 73%, 64% and 79%. Given the discontinuation curves these are applied to, they underestimate the direct drug costs of docetaxel, cabazitaxel and radium-223 for 1st line mCRPC.

[1] As reviewed later, an adjustment is applied to the costs of abiraterone for 1st line mCRPC with the intention of allowing for the [redacted], but this has little to no effect and can be ignored.

As far as the ERG can ascertain, the 1st line mCRPC treatment costs are calculated as the prevalent 1st line mCRPC on treatment population multiplied by a time invariant arm specific

Table 46 Scenario analyses around MSM start point: AAP+ADT cost effectiveness

	MSM/TA387 model		MSM model	
KM cut-off	vs ADT	vs DOC + ADT	vs ADT	vs DOC + ADT
4 months	£16,936	£17,180	£19,884	£26,001
5 months (BC)	£17,418	£17,828	£20,438	£26,909
6 months	£17,638	£18,358	£20,636	£27,619
7 months	£17,825	£19,326	£21,001	£28,545

5.2.11 Model validation and face validity check

DOC+ADT vs ADT estimates

The NICE summary of DOC+ADT compared to ADT for mHSPC states that "*In men with hormone-sensitive metastatic prostate cancer at 4 years, estimates based on a meta-analysis of the 3 RCTs (STOpCaP, n=2992)… a 9% absolute improvement in overall survival with docetaxel compared with ADT alone (49% compared with 40%, p<0.0001)… a 16% absolute improvement in time to disease progression with docetaxel compared with ADT alone (treatment failure 64% compared with 80%, p<0.0001)".*

The company base case predicts survival at 4 years of 47% for DOC+ADT compared to 34% for ADT, so a similar absolute survival for DOC+ADT but somewhat lower for ADT and hence a larger net gain of 13%. The company outline that this comparison is based upon the STOpCaP NMA and in a broader population that the licensed indication for AAP+ADT in newly diagnosed high-risk mHSPC. Taking rPFS as the measure of progression the company base case predicts progression at 4 years of 75% for DOC+ADT and 87% for ADT suggesting that the model overestimates progression for both arms and particularly for DOC+ADT. Linking the OS and rPFS together may suggest that the model overestimates the time that DOC+ADT patients spend in post progression survival. Given the importance of post progression mCRPC costs in the DOC+ADT arm for the company base case, any overestimation of the time spent in post progression in the DOC+ADT arm may of concern.

Additional ERG structural analysis

The company scenario analysis that uses the MSM model rather than the MSM/TA387 model also revises the mCRPC treatment proportions to be those of the LATITUDE trial. The company argument is that the LATITUDE data were generated by these mCRPC treatment proportions. The results of this scenario analysis can be compared with the results of a

Most of the values in the above are in line with intuition when compared with the TPMs of AAP+ADT and ADT. However, the probability of dying among those who have progressed is anomalous and is now lower than that of both AAP+ADT and ADT. It can be argued that this anomaly is worse than that of the DOC+ADT TPM of the company base case.

Application of the above TPM considerably worsens the deterministic MSM/TA387 model cost effectiveness estimate for AAP+ADT compared to DOC+ADT from £17,828 per QALY to £25,530 per QALY. The ERG implementation of sampling of this within the probabilistic modelling may be formally incorrect and may not properly take into account confidence intervals and correlations. Nonetheless, this results in a smaller change in the central probabilistic estimate, it only worsening from £18,168 per QALY to £20,867 per QALY. The non-linearity of the model may relate to the DOC+ADT versus ADT OS hazard ratio being somewhat further from unity than the DOC+ADT versus AAP+ADT hazard ratio.

The above does not argue that the company choice is incorrect. It only highlights that it is a choice which has not been justified, another choice could equally well have been made and that the most reasonable estimate may lie somewhere between the two.

MSM/TA387 model: Differentiation of 1st line mCRPC treatment effects

As already highlighted, the company comparison of 1st line mCRPC treatments' effectiveness estimates an OS hazard ratio central estimate which [redacted]

The company MSM/TA387 model structure is largely justified by the company on the basis of the need to properly model the effects of extending rPFS upon OS; i.e., the LATITUDE data for rPFS are reliable but thereafter the modelling needs to depart from the LATITUDE data.

The only means of approximating this within the MSM/TA387 model is to differentiate 1st line mCRPC treatments by the company central estimates of the OS hazard ratios. The ERG will apply this as a sensitivity analysis.