HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cabazitaxel for treating hormone-relapsed metastatic prostate cancer after a docetaxel-containing regimen (review of TA255) [ID889]

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Sanofi
   - British Uro-Oncology Group
   - Royal College of Physicians (on behalf of the NCRI-RCP-ACP-RCR)
     The Department of Health indicated that they had no comments to make on the ACD

3. **Comments on the Appraisal Consultation Document from experts:**
   - Allan Higgin, patient expert nominated by the Prostate Cancer Support Organisation

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **ERG Critique of the extra information submitted by Sanofi**

6. **Email from NHS England regarding potential pricing structure for cabazitaxel in prostate cancer which includes a PAS**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Cabazitaxel for hormone relapsed metastatic prostate cancer treated with docetaxel

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Sanofi	**Patients eligible for cabazitaxel in light of the End of Life (EoL) criteria**. We agree with the Appraisal Committee that patients treated with the Androgen Receptor Targeted Agents (ARTA), abiraterone or enzalutamide, ahead of docetaxel, form the majority (~70%) of patients eligible for cabazitaxel and that the EoL criteria apply to this setting. However, we would also urge the Appraisal Committee to consider a small but important population of patients (~15%) who have not received ARTA treatments prior to docetaxel but for whom the use of ARTA treatments post-docetaxel is unlikely to be of benefit. This might be due to the nature of their disease, for example if they have a high burden of metastases, experience rapid progression during or after docetaxel (aggressive disease), or a poor or transient response to earlier Androgen Deprivation Therapy (ADT) (see Appendix 1). In these patients, cabazitaxel has been shown to be active. (1-13) It is because these patients have few other options beyond BSC (Radium-223, for example, is contraindicated in patients with bone and visceral metastases) that they remain at high unmet need and not specifically recognised in the present recommendations. We propose that cabazitaxel would meet the End of Life (EoL) criteria when used in this patient group, and its cost-effectiveness should be examined in this context.	Thank you for your comments. Please see section 4.3 of the final appraisal determination (FAD).

Consultee	Comment [sic]	Response
	The eligible patients for consideration under EoL criteria are those not suitable for ARTA treatments; these include: Patients already treated with ARTA before progressing on docetaxel treatment Patients not previously treated with ARTA, but for whom ARTA is unlikely to provide benefit. These patients are likely to have: Poor or transient response to earlier Androgen Deprivation Therapy (ADT). Rapid progression during or after docetaxel exposure (aggressive disease). A high burden of metastases. For these patients, the only non-palliative treatment option is cabazitaxel.	Thank you for your comments. Please see section 4.3 of the FAD.
	The most appropriate source of evidence to support the Appraisal Committee decision on cabazitaxel compared to BSC. Mitoxantrone has been considered by the Committee to be equivalent to BSC and the Committee has stated that cabazitaxel is a beneficial treatment option versus BSC when using evidence from the direct trial based comparison (TROPIC trial). This is the evidence that informed the ERG base-case ICERs for the assessment of cost-effectiveness versus BSC as described in section 4.19 in the ACD. However, in section 4.20 of the ACD, the Committee relies on the ERG assessment that uses the Network Meta-Analysis (NMA), to inform its decisions on the cost-effectiveness of cabazitaxel compared to BSC in the group not receiving ARTA before docetaxel. In light of the inconsistency and uncertainty surrounding the comparison to BSC resulting from the NMA (sections 4.8, 4.9 and 4.20), which was conducted primarily to facilitate comparison with abiraterone and enzalutamide, we believe it is not appropriate to use this indirect data to inform the key decision for the committee on the cost-effectiveness of cabazitaxel versus BSC in this group. We suggest that the ERG base-case comparison using TROPIC data directly is more appropriate.	Thank you for your comments. Please see section 4.13 of the FAD.

Consultee	Comment [sic]	Response
	New patient access scheme and cost effectiveness analysis. Following the review by the ERG, and the Appraisal Committee's expressed preferences for the modelling approach, we recognise that the ERG base-case ICER for cabazitaxel falls above the threshold for ICERs generally considered acceptable for medicines meeting the EoL criteria. To remedy this, we have agreed an adjustment to the PAS with the Department of Health which should allow the Appraisal Committee to consider cabazitaxel a cost-effective use of NHS resources. (Appendix 2). Cost-effectiveness analysis incorporating the revised PAS (an increased discount from list price) and utilising the Appraisal Committee's preferred assumptions and ERG suggested amendments, results in a base-case ICER of £45,159 (deterministic) and £45,982 (probabilistic) (Appendix 2). We believe that these are the most probable ICERs for patients who have received the ARTAs ahead of docetaxel and also for those who have not had prior ARTA exposure but for whom clinicians would judge the ARTAs to be inappropriate after docetaxel. In both these cases patients would have no treatment options beyond BSC, and we believe the EoL criteria would therefore apply	Thank you for your comments. Please see sections 3.36 and 4.21 of the FAD.
	Supply of cabazitaxel. At the request of the Appraisal Committee we have worked with NHS England and at their suggestion, the British Oncology Pharmacy Association (BOPA), to provide assurances on the new supply route for cabazitaxel in terms of feasibility for the NHS and the implications for costs associated with wastage. We can now provide this assurance to the Committee in the form of a direct communication from NHS England which supports the supply arrangements described by Sanofi, and have provided a copy of this communication and further details in Appendix 3 below. In light of these assurances, we believe the circumstances in which medicines wastage can be minimised can be routinely met, and therefore the most appropriate analysis to support the Committee in their decision-making will be those presented in which the drug wastage is removed (i.e. cost per mg analyses).	Thank you for your comments. Please see section 4.19 of the FAD.

Consultee	Comment [sic]	Response
British Uro-oncology Group	**The British Uro-oncology Group (BUG) fails to understand NICE's preliminary recommendation** that:1.1 Cabazitaxel in combination with prednisone or prednisolone is not recommended within its marketing authorisation for treating hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen. BUG strongly urges NICE to re-consider its ACD recommendation. In England, the uptake of cabazitaxel through the National Cancer Drugs Fund (NCDF) clearly demonstrates the unmet need for this group of patients and the use is across the country with no significant geographical variation	Thank you for your comments. Please see section 1.1 of the FAD.
	Due to the heterogeneity of prostate cancer, it is essential that oncologists are able to select the most appropriate therapies for men with metastatic castration resistant prostate cancer (mCRPC) in order to allow optimal treatment. Evidence indicates that cabazitaxel is active in mCRPC and is likely to be optimal therapy for those men with AR-V7 positive mCRPC cases	Thank you for your comments. Please see section 4.3 of the FAD.
	There are no robust randomised trials to address the optimum sequencing of treatments for mCRPC. The meta-analysis of 10 published sequencing studies shows that overall survival is significantly better in patients with mCRPC who receive 3 agents (docetaxel, abiraterone and cabazitaxel) compared to those who receive 2 agents (docetaxel and abiraterone). (Maines F et al. ASCO GU 2015 (abstract 258)	Thank you for your comments. Please see sections 1.1 and 4.23 of the FAD.
	Patients in STAMPEDE who are currently receiving early docetaxel as standard of care and enzalutamide/abiraterone as their trial option would have no further chemotherapy management option when they develop mCRPC. The ethics should be questioned around whether patients should consent to enter a trial now if they will have no management options or fewer treatment options in the future.	Thank you for your comments. Please see sections 1.1 and 4.23 of the FAD.
	Finally, it is important to highlight that the role of cabazitaxel is different from that of radium-223 in the mCRPC setting and the benefits demonstrated for cabazitaxel are not limited to patients with bone metastases only.	Thank you for your comments. Please see section 4.31 of the FAD.

Consultee	Comment [sic]	Response
The Royal College of Physicians	The proposal to not recommend cabazitaxel appears to be based on health economic considerations rather than clinical effectiveness. Our clinical experts do not have the necessary expertise to comment on the health economic analyses. However, they feel strongly that cabazitaxel is an effective and well tolerated agent in the treatment of men with metastatic castration-resistant prostate cancer. It has become widely used throughout the world as a standard treatment and in the UK via the CDF. Overall, we believe it would be highly regrettable if the drug were no longer to be available to UK patients. Both professional and patient groups would be extremely disappointed	Thank you for your comments. Please see section 1.1 of the FAD.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Prostate Cancer Support Organisation	I am deeply disappointed by the provisional recommendations made in the Appraisal Consultation Document 'Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen'. We, the Patient Representatives, were not given any real opportunity to express the important part that Cabazitaxel plays in improving the quality of life, postponing death, and providing the consequential extension to family life. It is heart-rending to witness the mental anguish, confusion and dismay men and their families suffer trying to obtain 'end-of-life' drugs, the availability of which are subject to the vagaries of processes such as this. These families are at a very vulnerable stage in their lives, or should I say deaths, and the stress, fatigue, pressure and turmoil this uncertainty places on them is cruel. To write more would, I feel be fruitless, as it is apparent that the opinion and input of Patient Representatives and the many cancer suffers they represent, is of little value or importance to the decision making process. In consequence neither I, nor the charity I represent, the Prostate Cancer Support Organisation, can begin to support the provisional recommendations or consider them to have been arrived at following an adequate appraisal process.	Thank you for your comments. The committee considered carefully the written submissions from patient groups and a patient expert, and the testimony from patient experts during the meeting. The committee also discussed the responses to consultation, and it recognised that it is important to have a choice of treatments (see FAD sections 4.4 and 4.30). Having considered all of the evidence carefully, the committee decided to recommend cabazitaxel (see section 1.1 of the FAD).

No comments received from commentators

Comments received from members of the public

Role*	Section	Comment [sic]	Response

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
NHS Professional - consultant oncologist caring for men with prostate cancer		This document fails to acknowledge the heterogeneity of prostate cancer. There are compelling data that using a one sized fits all approach will neither benefit treatments nor utilise resource efficiently as patients will receive ineffective treatment in the absence of clinician choice . There are multiple subtypes of prostate cancer on biopsies of which approx. 40% are thought to have mutations or specific gene expressions that confer resistance to androgen targeted agents. Small et al , Bova et al JAMA 2015) In particular Antonarakis (NEJM 2014, JAMA 2015)has demonstrated that Androgen receptor pathways with the variant AR7 receptor are relatively resistant to Androgen receptor targeted agents unlike taxane therapy. Watson et al (Nature Reviews Cancer Nov 2015) have highlighted the development of multiple factors in development of resistance to Androgen receptor targeted agents. The use of abiraterone or enzalutamide in these men post docetaxel chemotherapy will therefore confer neither a survival nor symptomatic benefit and will waste resource , leaving this patient group with no treatment available other than best supportive care. The use of palliative radiotherapy for symptoms of pain, visits to primary care and prescriptions for analgesia will thus increase and complications of advanced disease such as spinal cord compression and pathological fractures will place additional burdens on the NHS and social care. The use of palliative radiotherapy for symptoms of pain, visits to primary care and prescriptions for analgesia will thus increase and complications of advanced disease such as spinal cord compression and pathological fractures will place additional burdens on the NHS and social care.	Thank you for your comments. The committee was not presented with evidence about the efficacy of cabazitaxel for different genetic subtypes of prostate cancer. It did appreciate that prostate cancer is a heterogeneous disease and it is important to have a choice of treatments so that the most suitable one can be selected for each individual (see section 4.30 of the FAD).

Role*	Section	Comment [sic]	Response
NHS Professional		Radium 223 is not indicated for men with incipient/occult very recently treated spinal cord compression, or for men with nodal disease greater than 2cm or those with visceral metastases. An entire patient group with effective disease is thus without second line therapy. These men meet end of life criteria as they have no treatment options without the potential of second line chemotherapy Cabazitaxel retains activity after androgen receptor targeted therapies (Pezaro et al European Urology 2014) unlike the ineffective sequencing of one androgen receptor targeted agents after another (Baimchini et al EJC 2013)	Thank you for your comments. Please see sections 4.2 and 4.24–4.27 of the FAD.
NHS Professional		The UK 5 centre pooled data ECLIPSE (Real life treatment sequences and survival of men with mCRPC receiving cabazitaxel in UK clinical practice) (presented ESMO 2015, ESMO Asia 2015, Pan et al) has shown that 3 sequential treatments in patients with mCRPC offered survival gain over two sequential therapies. Single centre data from the Rosemere Cancer Centre (Pan et al 2015 ESMO ASIA) indicated that the Doc- Cab-Ab offered improved survival over Doc, Ab, Cab although in the pooled analysis for 5 centre in ECLIPSE, the survival results were very similar irrespective of which sequence was used. However, three sequential treatments offered significant gain. Without clinician choice of appropriate therapy and with a simplistic one size actually fits none approach, the gains made in prostate cancer outcomes since 2005 will be lost as for 40% of our patient group there will be no effective second line options available, a position men with prostate cancer were in 10 years ago.	Thank you for your comments. Please see sections 4.2 and 4.3 of the FAD. The committee accepted that prostate cancer is a heterogeneous disease and it is important to have a choice of treatments so that the most suitable one can be selected for each individual (see section 4.30 of the FAD).

Role*	Section	Comment [sic]	Response
Patient		I am very concerned that at present you are not minded to approve cabazitaxel for use in the NHS. This drug offers a valuable second-line chemotherapy for advanced prostate Ca. patients where all else has failed, and has been shown to extend life and improve quality of life, factors highly valued by patients as they reach the end of life. Failure to approve cabazitaxel removes all hope and discriminates against men who have nowhere else to turn. I urge you to reverse your interim decision.	Thank you for your comments. Cabazitaxel is now recommended as a treatment option. Please see section 1.1 of the FAD.
NHS Professional		There are a proportion of patients with metastatic hormone refractory prostate cancer who do not respond durably to initial hormone treatment. After docetaxel chemotherapy, these patients have the NICE approved options of enzalutamide or abiraterone availabel to them. Neither of these agents is effective in patients who have had a poor response to first line androgen deprivation. Cabazitaxel is well tolerated, and would be a useful option for these patients.	Thank you for your comments. Cabazitaxel is now recommended as a treatment option. Please see section 1.1 of the FAD.

Role*	Section	Comment [sic]	Response
NHS Professional		We write to express our disappointment and concerns regarding the recent ACD on cabazitaxel and note that: ˜Cabazitaxel does not provide enough benefit to patients to justify its high cost even when the special considerations were applied, so NICE did not recommend it. We were involved with the original TROPIC trial and the subsequent EAP programme. Since then we have prescribed this medicine to numerous patients and have found it to be effective in both offering life extension and also palliative benefit to a number of patients. Removing this medicine would constrain our ability to treat patients efficiently. Moreover the greatest impact will be on patients who have aggressive prostate cancer that has responded poorly to LHRH analogue therapy or indeed docetaxel treatment. These patients are unlikely to respond to enzalutamide or abiraterone treatment. Cabazitaxel has Level 1 efficacy evidence; indeed most of the patients entering the TROPIC Phase III study had docetaxel resistant disease and/or progression in 70% within 3 months. Therefore they were a group of patients with a very poor prognosis. We therefore ask you to reconsider the scientific evidence for this medicine and review your decision in a patient sub group that clearly has an unmet need.	Thank you for your comments. Cabazitaxel is now recommended as a treatment option. Please see section 1.1 of the FAD.

Role*	Section	Comment [sic]	Response
NHS Professional		Cabazitaxel is a drug which provides a unique role in the treatment of prostate cancer. It has demonstrated an unequivocal overall survival advantage in patients who have progressed after Docetaxel chemotherapy. The great majority of patients will now have had either Abiraterone or Enzalutamide prior to receiving or after Docetaxel chemotherapy. A significant proportion remain, fit and enjoy a reasonable quality of life despite progressive disease. In this cohort of patients who have had Abiraterone/Enzalutamide and progressed after Docetaxel, Cabazitaxel is the only effective treatment option (for patients with bone only disease, Alpharadin could be considered but a significant majority of patients have bone and soft tissue disease). The difficulty in assessing evidence in this setting (as in many cases) is that the main data supporting Cabazitaxel comes from a study which pre-dates the use of both Abiraterone and Enzalutamide. In clinical practice, in our large academic institution, the great majority of patients in whom we use Cabazitaxel would have already had either Abiraterone or Enzalutamide, either pre or prior to Docetaxel. It is not currently clear from the clinical evidence what the best sequencing for these drug are. In routine clinical practice around the country, it does vary as to who provides Docetaxel and who provides Abiraterone or Enzalutamide first. In our practice, we find Cabazitaxel to be effective in castrate resistant post-Docetaxel setting irrespective of whether the patients have had Docetaxel pre or post Enzalutamide/Abi. I note the comments on Cabazitaxel being extendedly dominated by Enzalutamide but no reference to Abiraterone in the setting?	Thank you for your comments. Cabazitaxel is now recommended as a treatment option. Please see section 1.1 of the FAD.

Role*	Section	Comment [sic]	Response
		There appears to be significant emerging data about resistance to both Abiraterone and Enzalutamide. In this cohort of patients (a poor prognosis group) there seems to be a clear advantage to have two chemotherapy drugs of both which have shown a survival advantage. Although not yet tested in clinical trials, there are a number of trials and development to test Cabazitaxel in the setting, as it is our clinical experience that it is effective where both Abiraterone and Enzalutamide resistance is present. With the use of Docetaxel in the hormone sensitive setting (based on Stampede trial data), there will be a general shift in practice as to when Docetaxel is used. It will result in Docetaxel being used prior to Abiraterone or Enzalutamide in the hormone sensitive setting. In my view, this would wrongly potentially preclude the use of Cabazitaxel later in the disease process, as patients would not have had Abiraterone or Enzalutamide œprior to Docetaxel. I would encourage NICE to negotiate with the company to consider reducing the cost of the drug to bring it below the required QALY as the loss Cabazitaxel would be disadvantageous to our patients who currently have the benefit of the treatment with a clear survival advantage.	Thank you for your comments. Please see section 4.3 of the FAD. Please see section 4.23 of the FAD.
Patient		My husband was on cabazitaxel last year and had no side effects. It enabled us to carry out a full and active life whilst under going the treatment and increased his life expectancy. Please do not discontinue the availability of this drug - it would be a great loss to prostate sufferers.	Thank you for your comments. Cabazitaxel is now recommended as a treatment option. Please see section 1.1 of the FAD.
Patient		Cabazitaxel is the reason I'm alive today and able to write this. It was the one form of chemotherapy that had a dramatic and positive effect on my prostate cancer - with few side-effects - after other treatments had failed. It must remain available for the thousands of other sufferers in my situation. Please!	Thank you for your comments. Cabazitaxel is now recommended as a treatment option. Please see section 1.1 of the FAD.

Meindert Boysen,
Programme Director Technology Appraisals
Centre for Health Technology Evaluation
National Institute for Health and Care Excellence,
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

19th February 2016.

Dear Meindert,

Re. NICE review of TA255 (Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen)

Thank you for the opportunity to comment upon the NICE draft decision for cabazitaxel in hormone refractory metastatic prostate cancer (mHRPC). Whilst we are disappointed that the preliminary decision of the Appraisal Committee was not to recommend cabazitaxel, we are encouraged that the Committee has recognised the needs of people with mHRPC who have few remaining treatment options.

Our response focuses on addressing the key issues highlighted by the Appraisal Committee and our principal concerns with respect to the interpretation of the available evidence. Our response addresses the following:

1. Clarification regarding the population eligible for cabazitaxel under the EoL criteria
2. The most appropriate evidence for comparisons of cabazitaxel versus BSC.
3. An increased discount in the new PAS and new cost-effectiveness results.
4. NHS England endorsement of the no wastage supply arrangement for cabazitaxel.

Minor factual inaccuracies are noted in Appendix 4.

1. Patients eligible for cabazitaxel in light of the End of Life (EoL) criteria (See also Appendix 1).

We agree with the Appraisal Committee that patients treated with the Androgen Receptor Targeted Agents (ARTA), abiraterone or enzalutamide, ahead of docetaxel, form the majority (~70%) of patients eligible for cabazitaxel and that the EoL criteria apply to this setting. However, we would also urge the Appraisal Committee to consider a small but important population of patients (~15%) who have not received ARTA treatments prior to docetaxel but for whom the use of ARTA treatments post-docetaxel is unlikely to be of benefit. This might be due to the nature of their disease, for example if they have a high burden of metastases, experience rapid progression during or after docetaxel (aggressive disease), or a poor or transient response to earlier Androgen Deprivation Therapy (ADT) (see Appendix 1). In these patients, cabazitaxel has been shown to be active. (1-13) It is because these patients have few other options beyond

BSC (Radium-223, for example, is contraindicated in patients with bone and visceral metastases) that they remain at high unmet need and not specifically recognised in the present recommendations. We propose that cabazitaxel would meet the End of Life (EoL) criteria when used in this patient group, and its cost-effectiveness should be examined in this context.

The eligible patients for consideration under EoL criteria are those not suitable for ARTA treatments; these include:

- Patients already treated with ARTA before progressing on docetaxel treatment
- Patients not previously treated with ARTA, but for whom ARTA is unlikely to provide benefit. These patients are likely to have:
    - Poor or transient response to earlier Androgen Deprivation Therapy (ADT).
    - Rapid progression during or after docetaxel exposure (aggressive disease).
    - A high burden of metastases.

For these patients, the only non-palliative treatment option is cabazitaxel.

2. The most appropriate source of evidence to support the Appraisal Committee decision on cabazitaxel compared to BSC. (See also Appendix 1).

Mitoxantrone has been considered by the Committee to be equivalent to BSC and the Committee has stated that cabazitaxel is a beneficial treatment option versus BSC when using evidence from the direct trial based comparison (TROPIC trial). This is the evidence that informed the ERG base-case ICERs for the assessment of cost-effectiveness versus BSC as described in section 4.19 in the ACD.

However, in section 4.20 of the ACD, the Committee relies on the ERG assessment that uses the Network Meta-Analysis (NMA), to inform its decisions on the cost-effectiveness of cabazitaxel compared to BSC in the group not receiving ARTA before docetaxel. In light of the inconsistency and uncertainty surrounding the comparison to BSC resulting from the NMA (sections 4.8, 4.9 and 4.20), which was conducted primarily to facilitate comparison with abiraterone and enzalutamide, we believe it is not appropriate to use this indirect data to inform the key decision for the committee on the cost-effectiveness of cabazitaxel versus BSC in this group. We suggest that the ERG base-case comparison using TROPIC data directly is more appropriate.

3. New patient access scheme and cost effectiveness analysis (See also Appendix 2).

Following the review by the ERG, and the Appraisal Committee's expressed preferences for the modelling approach, we recognise that the ERG base-case ICER for cabazitaxel falls above the threshold for ICERs generally considered acceptable for medicines meeting the EoL criteria. To remedy this, we have agreed an adjustment to the PAS with the Department of Health which should allow the Appraisal Committee to consider cabazitaxel a cost-effective use of NHS resources. (Appendix 2).

Cost-effectiveness analysis incorporating the revised PAS (an increased discount from list price) and utilising the Appraisal Committee's preferred assumptions and ERG suggested

amendments, results in a base-case ICER of £45,159 (deterministic) and £45,982 (probabilistic) (Appendix 2). We believe that these are the most probable ICERs for patients who have received the ARTAs ahead of docetaxel and also for those who have not had prior ARTA exposure but for whom clinicians would judge the ARTAs to be inappropriate after docetaxel. In both these cases patients would have no treatment options beyond BSC, and we believe the EoL criteria would therefore apply.

4. Supply of cabazitaxel (See also Appendix 3).

At the request of the Appraisal Committee we have worked with NHS England and at their suggestion, the British Oncology Pharmacy Association (BOPA), to provide assurances on the new supply route for cabazitaxel in terms of feasibility for the NHS and the implications for costs associated with wastage. We can now provide this assurance to the Committee in the form of a direct communication from NHS England which supports the supply arrangements described by Sanofi, and have provided a copy of this communication and further details in Appendix 3 below. In light of these assurances, we believe the circumstances in which medicines wastage can be minimised can be routinely met, and therefore the most appropriate analysis to support the Committee in their decision-making will be those presented in which the drug wastage is removed (i.e. cost per mg analyses).

The Appraisal Committee heard from the patient experts that they value highly treatments that extend life, are well tolerated and offer improved quality of life. As such cabazitaxel is regarded as an important option for the treatment of mHRPC by patients and clinicians alike where BSC is the only alternative.

In this consultation response, we have sought to address the key concerns of the Appraisal Committee, both in terms of ensuring that cabazitaxel can be supplied efficiently and without wastage, and adjusting the PAS so that the Committee can be confident that cabazitaxel represents a cost-effective use of NHS resources. We hope that the Committee are now able recommend this medicine for use in the NHS as an alternative to BSC for patients with mHRPC.

Yours Sincerely,

Dr Charlie Nicholls
Head of Health Outcomes

Appendices

Appendix 1 – Population considerations.

Table 1. Description of the populations not suited to treatment with other agents.

Key response area	Rationale	Solution
Sections 4.24 / 4.28. Abiraterone and enzalutamide. The committee have concluded that the EoL considerations do not apply to the population of people who have not been previously treated with abiraterone or enzalutamide.	Implicit in this conclusion is the notion that these patients all have similar baseline characteristics and the same propensity to benefit from the various treatments. Hence all these patients might be expected to be equally suited to any of the therapies. In reality this is more complex, because of the heterogeneous nature of prostate cancer. The Committee heard from the experts that a single therapeutic choice is not appropriate for everybody. Clinicians will identify the 'chemotherapy patient' using clinical judgement based on prognostic characteristics. For many of these patients, the ARTA therapies are not a relevant option. Such prognostic factors are outlined below: **Poor response or rapid progression on primary Androgen Deprivation Therapy (ADT).** • Abiraterone and enzalutamide (mCRPC) interrupt the production of testosterone (by the tumour) which means they work only on tumours with some sensitivity to hormones. • During disease progression multiple chromosomal changes occur over time and can be different between different tumour sites in the same patients indicating that single treatment plan is not be suitable for all patients with Prostate Cancer.(14) • The development of resistance in Prostate Cancers to hormonal therapy is now well understood.(14) For example ARv7+ve tumours show limited response to advanced hormonal therapies and exhibit resistance.(15) Primary resistant tumours already exhibit resistance at the outset, but secondary resistance can develop over time as the ARv7+ve tumour cells become more dominant as ARv7-ve tumour cells are eliminated by hormone therapy to which they are sensitive. • Short time to castration resistance (less than 12 months) is associated with poorer activity of ARTA in men with mCRPC.(16) (50% PSA response was 16% and 41% with prior ADT treatment of <12 months and >12 months respectively).	Considering these prognostic factors we suggest that suitability for treatment with the androgen targeted therapies should be considered in the recommendation. In the small but significant population of people who have not been previously treated with abiraterone or enzalutamide but for whom these agents might be considered inappropriate by clinicians, there are few other options beyond BSC. Hence for these patients we suggest that the EoL considerations apply.

	• The mechanism of action of cabazitaxel is not androgen dependent.(17;18) This means it not only works on hormone sensitive cell lines, but it also works on the aggressive clones which do not respond to ARTAs. The efficacy of cabazitaxel does not seem to be influenced by the duration of prior ADT before docetaxel treatment.(19) • These issues are highlighted in recent Danish guidelines which recommend that any fit patient responding less than 12 months to ADT should move straight to chemotherapy.(20) **Patients with more aggressive disease** • In a retrospective study of patients receiving cabazitaxel after progress during or after docetaxel treatment. A higher Gleason score (>8) appeared to be associated with prolonged PFS (HR0.36, 95% CI 0.18–0.72).(2) • Conversely, data from a French observational study on 381 patients treated with abiraterone after progression on docetaxel, identified a Gleason grade of 8–10 as an independent predictor of no response to treatment with abiraterone [Gleason 6/7 vs. 8–10, odds ratio (OR) 0.60, 95% CI 0.39–0.85](21) **Patients who have progressed on rapidly (within ~3 months) after docetaxel** • Cabazitaxel was developed to overcome docetaxel resistance(17) and has a different mechanism of action. TROPIC and subsequent studies have shown that cabazitaxel retains its activity after docetaxel treatment. It is noteworthy that in TROPIC, 70% of patients were refractory to docetaxel (progression during or within 3 months of docetaxel completion). • A subgroup analysis of the COU-AA-301 abiraterone study showed that progression on abiraterone in patients who had stopped previous docetaxel due to progressive disease was quicker than those who had stopped docetaxel for other reasons. (14.2 months vs. 17.0 months)(22) • Further, the authors of a UK study which examined the response to abiraterone in mCRPC patients whose disease had progressed early on docetaxel suggest that '*patients who are refractory to docetaxel do not respond to abiraterone'(23)* • Reports suggest that the clinical activity of enzalutamide in docetaxel pre-treated	

	patients may be 'blunted' providing evidence of potential cross-resistance with docetaxel.(24;25) Due to the differing mechanism of action, cabazitaxel is thought not to exhibit the same degree of cross-resistance with AR targeted therapies(26)	
Section 4.2. Radium-223. The committee concluded that radium-223 is a valid comparator for patients with mCRPC.	Clinical and patient group opinion expressed at the committee meeting indicated that the cabazitaxel patient is not the same as the radium-223 patient on the basis of the burden of visceral metastases and the aggressiveness of their disease. These characteristics are reflected in the differences between the licenses for the two products: • Radium-223 is not indicated for patients with visceral metastases o Radium-223 is contraindicated in patients with liver metastases.11% of patients in TROPIC had liver metastases. • Radium-223 is not indicated for those with recently treated spinal cord compression • Radium-223 is only for use where the disease has spread to the bone and is causing symptomatic pain Clinical opinion indicated that radium-223 is useful in the relief of symptomatic pain caused by bone metastases whereas the mechanism of action of cabazitaxel is different as it targets tumour cell division. Cabazitaxel may be used in patients with a burden of visceral metastases. In order to compare the TROPIC and the COU-AA-301 and AFFIRM populations it was necessary for the modelling to synthesize a measure of radiographic PFS from the TROPIC data. A comparable measure is not available from the radium-223 study, ALSYMPCA. Hence to provide a formal indirect comparison of the ALSYMPCA and TROPIC studies is problematic and we believe would be uninformative. For all these reasons we provided a simple comparison of clinical trial survival estimates from the key registration trials within our MS to support the committee but have not presented a formal comparison of cabazitaxel and radium-223.	We maintain, as do the key clinical guidelines (27-29), that disease heterogeneity means patients need tailored treatment options to extend overall survival in mCRPC. Just as for the population unsuited to the ARTAs described above, clinical opinion based on prognostic or clinical factors is likely to distinguish between patients with the highest propensity to benefit from either cabazitaxel or radium-223

Table 2. Issues identified with the fully incremental analysis.

Key response area	Rationale	Solution
Section 4.20 / 4.8 / 4.9. Network meta-analysis (NMA). The committee have based their decision making for the comparison versus best supportive care (BSC) for those patients who have not had previous exposure to abiraterone or enzalutamide on the fully incremental analysis presented by the ERG. In the presence of contradictory evidence derived from the high quality phase 3 trial, TROPIC, and the acceptance by the committee of the equivalence of mitoxantrone with BSC, we believe that the head-to-head comparison provides a more appropriate platform upon which to judge the cost-effectiveness of cabazitaxel.	Whilst the fully incremental analysis was technically feasible we believe that to compare all the products in this way is not appropriate, not least due to the nature of the NMA discussed below. The ERG noted on page 87 of their report that the NMA results could only be used as an indication of the direction of treatment effects between the therapies but that the results should be treated with caution. This is echoed in the committee conclusion on page 23 of the ACD that the '*network meta-analysis may not be robust because of potential differences between trials in populations and control treatments* This is for the following reasons (See also Section 4.10 in the submission dossier and Appendix B, page 9) • The baseline patient characteristics of the patients entering each of the studies are not comparable. • The definition of Progression Free Survival (PFS) is markedly different between trials and represents a problem for the indirect comparison, and by extension the use of indirect PFS data in the economic model • Radiographic PFS (rPFS) was derived from the patient level data from TROPIC, as this end point was reported in both the COU-AA-301 and AFFIRM trial papers. Examination of the median time to rPFS in the three trials however, indicates the values of rPFS for the control arms are substantially different, indicating that for the purposes of the NMA they should not be considered equivalent. • The proportional hazards assumption may not hold for some of the comparisons. (See Fizazi(30) for the COU-301-AA study in abiraterone).	We believe that any comparison with BSC to inform the decision making of the committee should be based upon the key pivotal phase III clinical trial head to head comparison with mitoxantrone, rather than upon a network meta-analysis which is subject to uncertainty. Use of an indirect treatment comparison by definition means that evidence is discarded with respect to the original data and so where direct evidence exists it is preferred.
Section 4.20. Comparison with BSC. The indirect comparison with BSC made via the NMA which informs this analysis is	The use of the NMA to inform the analysis vs. BSC in the population of patients who have not received abiraterone or enzalutamide before docetaxel is inconsistent with the use of the direct evidence used to consider the population who have received these agents	The data from the TROPIC study which is a direct head-to-head comparison utilising the PFS end-

not appropriate given the existing head-to-head evidence available from the TROPIC study.	ahead of docetaxel. • TROPIC provides high quality head-to-head evidence for the beneficial treatment effect of cabazitaxel over mitoxantrone. • Mitoxantrone has been accepted by the committee as '*similar to best supportive care'* (Section 4.6 of the ACD) • There is no OS benefit with mitoxantrone over BSC however we reiterate that it does provide benefits in terms of quality of life and pain palliation(31) and so this comparison may provide a conservative estimate of the benefits of cabazitaxel. • The comparison with BSC made in the fully incremental analysis replies on the application of hazard ratios derived from the NMA to the BSC arm from TROPIC. • It is noted on page 133 of the ERG report that the ICERs comparing cabazitaxel with BSC are '*substantively greater'* than those comparing cabazitaxel with mitoxantrone. This disparity was ascribed to the questionable nature of proportionality between hazards and the heterogeneity inherent in the between study comparisons.	point specified in the study is the most appropriate way to examine the cost-effectiveness of cabazitaxel relative to BSC. Indeed, the TROPIC study may produce an underestimate of the advantage of mitoxantrone over BSC considering its known palliative effects.

Appendix 2 – New analyses

Change to the confidential discount

A new confidential discount to the price of cabazitaxel has been agreed with the Department of Health. The list price and details of the proposed scheme are provided in Table 3 below.

Table 3. Current list price and new PAS discount.

	List price and discount
Current UK list price(s)	Cabazitaxel 60 mg / 1.5 ml concentrate and solvent for infusion: £3696 per vial, £61.60 per mg.(32)
Updated discount	The Patient Access Scheme will be a simple confidential discount from the list price at the point of invoice. The PAS adjusted cost will be *Commercial in confidence information removed* per vial, *Commercial in confidence information removed* per mg.

Base-case incremental cost-effectiveness analysis results incorporating the new PAS

The updated base-case uses the ERG exploratory base-case assumptions listed in section 3.39 of the ACD. These are

- Do not model stopping treatment for reasons other than disease progression.
- Do not model a reduced utility value for the last 3 months of progressive disease.
- Use eMIT prices for generic drugs.
- Use UK clinical audit data to model the costs of post-progression treatment and the proportion of patients who have best supportive care.

A further modification has been adopted to the additional preference reported by the Appraisal Committee for piecewise curve fitting for overall survival with cabazitaxel (3.32 and 4.11) Finally, as noted in the ACD in section 3.25, we have now incorporated wastage for mitoxantrone, addressing the error in the original analysis. The updated base-case results are tabulated below. (Table 4).

Table 4 . Base-case results: cabazitaxel vs. mitoxantrone - SG: ECOG PS 0-1, tottax ≥225.

Technologies	**Cabazitaxel**	**Mitoxantrone**
Total costs (£)	*Commercial in confidence information removed*	*Commercial in confidence information removed*
Total LYG		
Total QALYs		
Incremental costs (£)	£10,682	
Incremental LYG	0.347	
Incremental QALYs	0.237	
ICER (£) versus baseline (QALYs)	£45,159	
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years		

A summary of costs by health state is provided in Table 5 below.

Table 5. Summary of costs by health state for the comparison versus mitoxantrone - SG: ECOG PS 0-1, tottax≥225.

Health state	Cost Cabazitaxel	Cost Mitoxantrone	Increment	Absolute increment	% absolute increment
Stable	*Commercial in confidence information removed*		*Commercial in confidence information removed*		
Progressive					
End-of-life costs					
Total			£10,682	£10,682	100%

Sensitivity analyses

Probabilistic sensitivity analysis

Figure 1. Cost-effectiveness plane based on 2000 probabilistic simulations

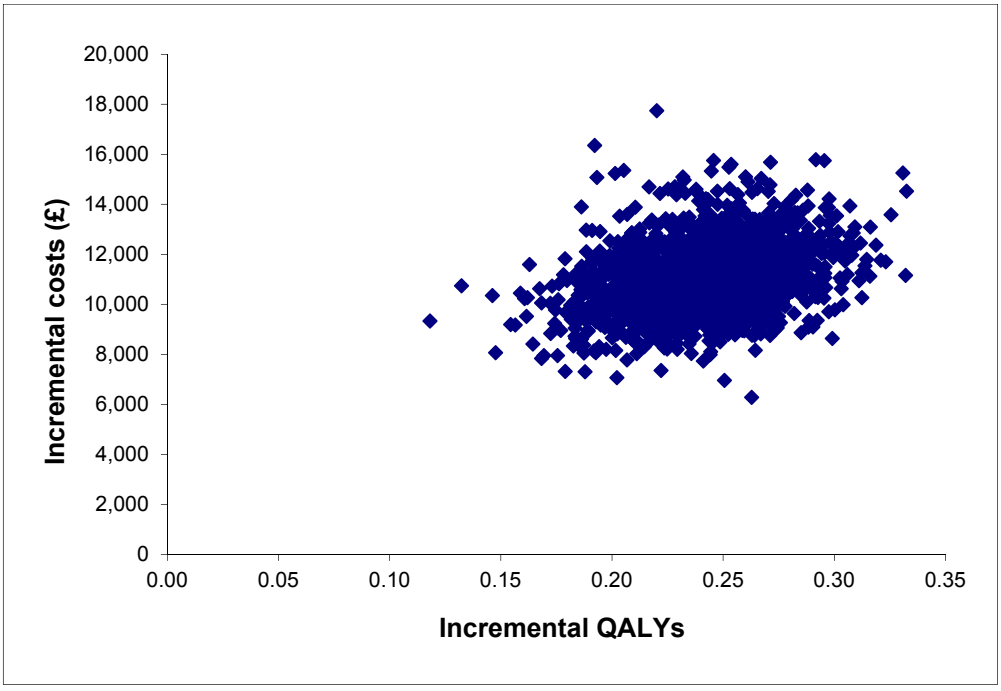
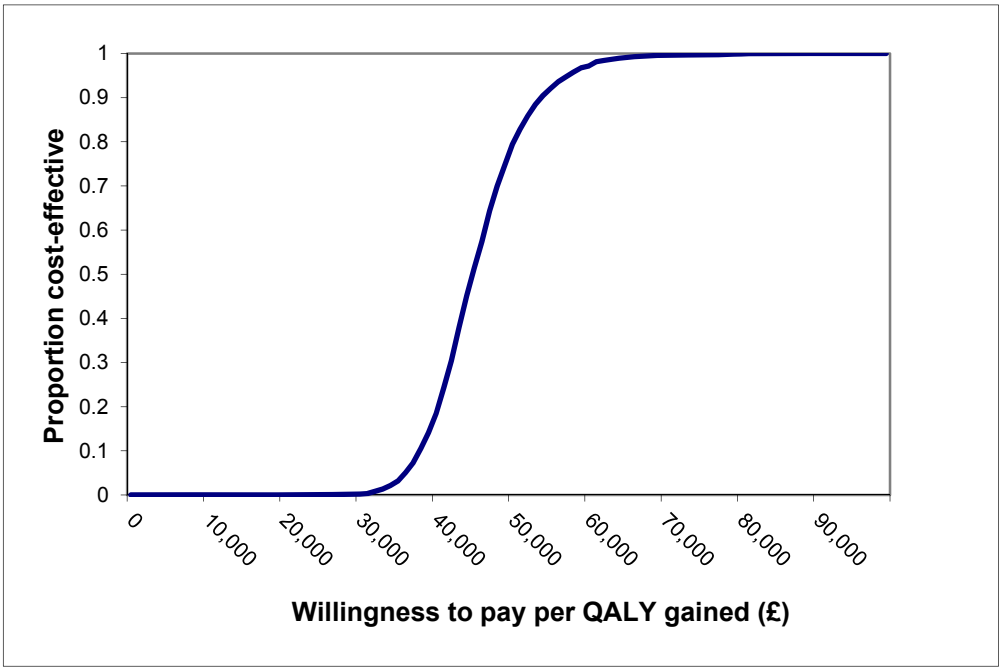


Figure 2. Cost-effectiveness Acceptability Curve (CEAC).



The probabilistic ICER is £45,982.

At a Willingness to Pay (WTP) threshold of £50,000/QALY the probability of cabazitaxel being a cost-effective treatment when compared to mitoxantrone is 75%.

One-way sensitivity analysis

Table 6. One-way sensitivity analyses for the comparison versus mitoxantrone - SG: ECOG PS 0-1, tottax≥225.

Sensitivity analysis	Incremental cost (£)	Incremental QALYs	Incremental LYs	ICER per QALY (£)	ICER per LY
Base-case	**10,682**	**0.237**	**0.347**	**45,159**	**30,754**
Utilities					
AE disutilities excluded	10,682	0.237	0.347	44,989	30,754
SD utility +20%	10,682	0.245	0.347	43,653	30,754
SD utility -20%	10,682	0.228	0.347	46,772	30,754
PD utility +20%	10,682	0.264	0.347	40,438	30,754
PD utility -20%	10,682	0.209	0.347	51,126	30,754
Time horizon					
3 years	9,892	0.192	0.278	51,445	35,617
5 years	10,617	0.233	0.342	45,582	31,060
Discount rates					
Costs: 0%, Effects: 0%	11,007	0.254	0.375	43,261	29,353
Costs: 3.5%, Effects: 0%	10,706	0.254	0.375	42,075	28,549
Costs: 0%, Effects: 3.5%	10,984	0.237	0.347	46,433	31,622

Sensitivity analysis	Incremental cost (£)	Incremental QALYs	Incremental LYs	ICER per QALY (£)	ICER per LY
Costs: 6%, Effects: 6%	10,467	0.225	0.329	46,568	31,799
	11,007	0.254	0.375	43,261	29,353
BSC as post-2nd line treatment for all arms					
Share of patients: 0%	11,597	0.237	0.347	49,025	33,387
Share of patients: 20%	11,368	0.237	0.347	48,058	32,728
Share of patients: 40%	11,139	0.237	0.347	47,092	32,070
Share of patients: 60%	10,911	0.237	0.347	46,125	31,412
Share of patients: 80%	10,682	0.237	0.347	45,158	30,753
Share of patients: 100%	10,453	0.237	0.347	44,192	30,095

Scenario analysis

Table 7. Additional scenario analyses for the comparison versus mitoxantrone.

Parameter/ Assumption	Base-Case	Scenario tested	Incr. Costs (£)	Incr. QALYs	ICER (£)
Base-Case			10,682	0.237	45,159
Overall Survival	OS 2yrs IPD-Weibull	OS 2yrs IPD- Exponential	11,526	0.293	39,317
		OS 2yrs IPD-Gompertz	10,333	0.213	48,519
		OS 2yrs IPD-Log logistic	11,635	0.302	38,550
		OS 2yrs IPD-Lognormal	12,668	0.371	34,162
Progression Free Survival	PFS Cab 2yrs IPD-Lognormal	PFS 2yrs IPD-Exponential	10,717	0.234	46,479
		PFS 2yrs IPD-Weibull	11,068	0.229	48,261
		PFS 2yrs IPD-Gompertz	10,992	0.227	48,491
		PFS 2yrs IPD-Log logistic	10,649	0.242	44,087
BSA	1.9	2.0	11,039	0.237	46,665
Pharmacist cost per cabazitaxel administration	15 minutes of pharmacist time required to order the appropriate dose of cabazitaxel	30 minutes of pharmacist time required to order the appropriate dose of cabazitaxel	10,737	0.237	45,389
Population	SG (ECOG 0-1, tottax≥225)	ITT	10,881	0.249	43,785
Proportion with G-CSF as primary prophylaxis	Caba 25% & Mitox: 10%	Caba 25% & Mitox: 0%	10,782	0.237	45,581

We have not reproduced the analyses for the comparisons versus abiraterone or enzalutamide as we are unaware of the confidential discounts offered for these products. We have provided the updated model as part of this response to allow the ERG to undertake further confidential analysis if required.

Appendix 3 – Compounding arrangements

A brief description of the compounding scheme is provided in Section 4.17 of the ACD. In response to the request by the committee, further details of the proposed scheme are provided below.

Sanofi has developed a service proposal for the supply of compounded cabazitaxel to NHS hospitals, with the aim of reducing wastage and enhancing the cost-effectiveness of treatment. This supply route is expected to be in place in Q2 2016.

The compounding supply service arrangements will operate as follows (subject to individual modifications):

- Sanofi will sell the licensed formulation of cabazitaxel (60mg vials), to a number of compounding companies already used by the NHS for the purpose of compounding product. The compounding companies will be required to have a Manufacturer's "Specials" Licence relating to the proposed activity.
- Sanofi will pay the compounding company a 'service fee' for the compounding service. No compounding fee will be payable by the NHS.
- The compounding company will receive orders in the normal way from NHS hospitals to prepare bags of cabazitaxel diluted for administration (prepared in accordance with the SmPC) at dosage specifications to meet the needs of particular NHS patients.
- The bags of compounded cabazitaxel, will be sold to NHS hospitals by the compounding companies at a price not to exceed the per milligram PAS price, in response to these orders.
- Sanofi will cover the costs of drug wastage.
- Sanofi will cover the costs of transport to NHS hospitals.
- Sanofi will cover the costs of a reasonable number* of returned unused bags.

* Based upon standard expectations of patient non-attendance or inability to receive dose

The committee also asked us to confirm with NHS England (NHSE) that this supply route can operate. This confirmation is provided below in a communication from Malcolm Qualie (Pharmacy lead, Specialised services, NHSE) received on the 17th February 2016.

Thank you for sharing your plans regarding a potential pricing structure for cabazitaxel in prostate cancer which includes a PAS.

I can confirm the cabazitaxel per mg drug supply service as described by Sanofi is both implementable across NHS England Trusts and will guarantee the removal of all drug wastage costs from the conversion of vials to dose specific patient infusion bags.

Specific areas which might cause issues have been managed through the design of the service: ensuring validated wastage of compounded bags is covered for justified patient non-attendance

or inability to receive dose, provision for multiple compounding vendors and for individual Trust pharmacy departments to act as vendors within the service should they not wish to engage a third party manufacturer. Some Trusts may have to organise blood tests to be carried out two days prior to the scheduled day of chemotherapy administration to ensure cell counts are sufficient for the patient to receive cabazitaxel, but this is not inconsistent with the trend towards more efficient chemotherapy services for patients in the NHS.

The proposed service could be improved through the use of dose-banded infusion bags as consistent with the current NHS England chemotherapy initiative and quality assurance of longer shelf-life of such dose banded infusion bags. This would enable significant IV chemotherapy service efficiencies. However, such provisions would require robust validation data which I understand is not currently available or appropriate for the manufacturer to adopt within the service, as it is not consistent with the existing cabazitaxel marketing authorisation.

Regards

Malcolm

Malcolm Qualie
Pharmacy Lead
Specialised Services
NHS England

Appendix 4 – Minor typographic errors and factual inaccuracies

Table 8. Typographical errors and corrections

Description of problem	Description of proposed amendment	Justification for amendment
Section 3.5 Page 6 the number of patients treated with previous chemotherapy is incorrectly reported: *'In the cabazitaxel group 71% of patients were previously treated with chemotherapy; this was 69% in the mitoxantrone group.'*	Suggested text change: *'All patients entering the study had previously received at least one chemotherapy regimen'*	As described in the ACD this refers to the proportion of patients previously treated with only 1 chemotherapy regimen and as such may be misleading. This has been taken in error from Table 19 in the submission document. Patients in TROPIC may have been treated with more than one chemotherapy regimen and the proportions of these are also shown in Table 19 of the submission document. The license for cabazitaxel is in patients who have previously received docetaxel containing regimens and so by definition all patients entering the trial had received previous chemotherapy.
Section 3.40 Page 16 There is a typographical error in bullet point 2. *'The probabilistic ICER was £51,849 per QALY gained (incremental costs Commercial in confidence information removed; incremental QALYs 0.23).'*	Suggested text change: *'The probabilistic ICER was £51,849 per QALY gained (incremental costs £12,133; incremental QALYs 0.23).'*	The incremental costs for the 'ERG probabilistic base-case (changes A1 to **A6**)' which **include** vial wastage (See table 13 in the first committee meeting pre-briefing document (PMB)) have been reproduced instead of the incremental costs for the 'ERG probabilistic base-case (changes A1 to **A5**)' which **do not** include vial wastage. The value should be £12,133.

Reference List

(1) Pezaro C.J. Response to cabazitaxel in CRPC patients previously treated with docetaxel and abiraterone acetate. J Clin Oncol 31[6], p. abstr 155. 2013.

(2) Buonerba C, Pond G.R., Sonpavde G, Federico P, Rescigno P, Puglia L, et al. Potential value of gleason score in predicting the benefit of cabazitaxel in metastatic castration-resistant prostate cancer. Future.Oncol. 9(6), 889-897. 2015.

(3) Fernandez O, Afonson J, Vazquez S, Campos B, Lazaro MLL, Anton Aparicio L.M. Metastatic castration-resistant prostate cancer: changing landscape with cabazitaxel. Anticancer Drugs 25[3], 237-243. 2014.

(4) Caffo O, de Giorgiu U, Zagonel V, Gasparro D, Fratino L, Facchini G, et al. Clinical Outcomes of Castration-resistant Prostate Cancer Treatments Administered as Third or Fourth Line Following Failure of Docetaxel and Other Second-line Treatment: Results of an Italian Multicentre Study. Eur.Urol. 68, 147-153. 2015.

(5) Caffo O, De GU, Fratino L, Alesini D, Zagonel V, Facchini G, et al. Clinical Outcomes of Castration-resistant Prostate Cancer Treatments Administered as Third or Fourth Line Following Failure of Docetaxel and Other Second-line Treatment: Results of an Italian Multicentre Study. Eur Urol 2015 Jul;68(1):147-53.

(6) Pezaro C.J., Omlin A.G., Altavilla A, Lorente D, Ferraldeschi R, Bianchini D, et al. Activity of cabazitaxel in castration-resistant prostate cancer progressing after docetaxel and next-generation endocrine agents. Eur Urol 2014 Sep;66(3):459-65.

(7) Sella A, Sella T, Peer A, Berger R, Frank S.J., Gez E, et al. Activity of Cabazitaxel After Docetaxel and Abiraterone Acetate Therapy in Patients With Castration-Resistant Prostate Cancer. Clin.Genitourin.Cancer 12[6], 428-432. 2014.

(8) Nakouzi N.A., Moulec S.L., Albiges L, Wang C, Beuzeboc P, Gross-Goupil M. Cabazitaxel Remains Active in Patients Progressing After Docetaxel Followed by Novel Androgen Receptor Pathway Targeted Therapies. Eur.Urol. 68, 228-235. 2015.

(9) Onstenk W, Sieuwerts AM, Kraan J, Van M, Nieuweboer AJ, Mathijssen RH, et al. Efficacy of Cabazitaxel in Castration-resistant Prostate Cancer Is Independent of the Presence of AR-V7 in Circulating Tumor Cells. Eur Urol 2015 Jul 15.

(10) van Soest R.J., Nieuweboer A.J., de Morree E.S., Chitu D, Bergman A.M., Goey S.H., et al. The influence of prior novel androgen receptor targeted therapy on the efficacy of cabazitaxel in men with metastatic castration-resistant prostate cancer. Eur J Cancer 2015 Aug 13.

(11) Maines F, Caffo O, Veccia A, Trentin C, Tortora G, Galligioni E, et al. Sequencing new agents after docetaxel in patients with metastatic castration-resistant prostate cancer. Crit Rev Oncol Hematol 2015 Aug 1.

(12) Sonpavde G, Bhor M, Hennessy D, Bhowmik D, Shen L, Nicacio L, et al. Sequencing of Cabazitaxel and Abiraterone Acetate After Docetaxel in Metastatic Castration-Resistant Prostate Cancer: Treatment Patterns and Clinical Outcomes in multicenter Community-Based US Oncology Practices. Clin.Genitourin.Cancer 13[4], 309-318. 2015.

(13) de Bono J.S., Oudard S, Ozguroglu M, Hansen S, Machiels J.P., Kocak I, et al. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational phase III trial (TROPIC). ASCO Annual Meeting.Chicago, USA . 2010.

(14) Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nature Reviews Cancer 2015;15:701-11.
(15) Antonarakis E.S., Lu C, Wang H, Luber B, Nakazawa M, Roeser J.C., et al. AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer. NEJM 37[1], 1028-1038. 2014.
(16) Loriot Y, Eymard JC, Patrikidou A, Ileana E, Massard C, Albiges L, et al. Prior long response to androgen deprivation predicts response to next-generation androgen receptor axis targeted drugs in castration resistant prostate cancer. Eur J Cancer 2015 Sep;51(14):1946-52.
(17) Vrignaud P, Lejeune D, Chaplin D. Preclinical profile of cabazitaxel. Drug Design, Development and Therapy 8, 1851-1867. 2014.
(18) European Medicines Agency. Assessment Report For Jevtana (cabazitaxel). Procedure No.: EMEA/H/C/002018. 20-1-2011. 29-9-2015.
(19) Oudard S, de Bono JS. Impact of cabazitaxel (Cbz) + prednisone (P; CbzP) on overall survival (OS) at 2 yrs and in patients (pts) with aggressive disease: post-hoc analyses of TROPIC trial. ESMO Congress 2012 [Poster 933P]. 2012.
(20) Radet for Anvendelse af Dyr Sygehusmedicin. Behandlingsvejledning med lægemiddelrekommandation for medicinsk behandling af metastatisk kastrationsresistent prostatacancer, mCRPC . 2015. 17-2-2016.
(21) Azria D, Massard C, Tosi D, Houede N, Joly F, Gravis G. An ambispective observational study in the safety and efficacy of abiraterone acetate in the French temporary authorizations for use (ATU): predictive parameters of response. J Clin Oncol 30[Suppl 5], 149. 2012.
(22) Chi KN, Scher HI, Molina A, Logothetis C, Jones RJ. Exploratory analysis of survival benefit and prior docetaxel (D) treatment in COU-AA-301, a phase III study of abiraterone acetate (AA) plus prednisone (P) in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 30[Suppl 15], Abstr 5. 2012.
(23) Mukherji D, Pezaro CJ, Bianchini D, Zivi A, de Bono J. Response to abiraterone acetate in the postchemotherapy setting in patients with castration-resistant prostate cancer whose disease progresses early on docetaxel. J Clin Oncol 30[Suppl 5], Abstr 17. 2012.
(24) Nadal R, Zhang Z, Rahman H, Schweizer MT, Denmeade SR, Paller CJ, et al. Clinical activity of enzalutamide in Docetaxel-naive and Docetaxel-pretreated patients with metastatic castration-resistant prostate cancer. Prostate 2014 Nov;74(15):1560-8.
(25) Chandrasekar T, Yang J.C., Gao A.C., Evans C.P. Targeting molecular resistance in castration-resistant prostate cancer. BMC Med 2015;13(1):206.
(26) van Soest RJ, de Morree ES, Kweldam CF, de Ridder CM, Wiemer EA, Mathijssen RH, et al. Targeting the Androgen Receptor Confers In Vivo Cross-resistance Between Enzalutamide and Docetaxel, But Not Cabazitaxel, in Castration-resistant Prostate Cancer. Eur Urol 2015 Jun;67(6):981-5.
(27) Basch E, Loblaw D.A., Oliver T.K., Carducci M, Chen R.C., Frame J.N., et al. Systemic therapy in men with metastatic castration-resistant prostate cancer:American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol 2014 Oct 20;32(30):3436-48.
(28) Parker C, Gillessen S, Heidenreich A, Horwich A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. Ann Oncol 2015 Sep;26 Suppl 5:v69-v77.
(29) European Association of Urology. Guidleines on prostate Cancer. 2015. 29-9-2015.

(30) Fizazi K, Scher H.I., Molina A, Logothetis C.J., Chi K.N., Jones R.J., et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012 Oct;13(10):983-92.
(31) Tannock I.F., Osoba D, Stockler M.R., Ernst D.S., Neville A.J., Moore M.J., et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J.Clin.Oncol. 14[6], 1756-1764. 1996.
(32) British national Formulary. Cabazitaxel. 1-9-2015. 29-9-2015.

22 February 2016

British Uro-oncology Group (BUG) Response to:

NICE Appraisal Consultation Document:
Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen

The British Uro-oncology Group (BUG) fails to understand NICE's preliminary recommendation that: *1.1 Cabazitaxel in combination with prednisone or prednisolone is not recommended within its marketing authorisation for treating hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen.*

BUG strongly urges NICE to re-consider its ACD recommendation. In England, the uptake of cabazitaxel through the National Cancer Drugs Fund (NCDF) clearly demonstrates the unmet need for this group of patients and the use is across the country with no significant geographical variation.

BUG is a well-established charity, representing the views and practice of oncologists across the UK. It is of critical concern that the ACD recommendation does not offer a treatment for those patients unsuitable for further hormone treatment following a docetaxel regime. The ACD clearly does not recognise the heterogeneity of prostate cancer.

Due to the heterogeneity of prostate cancer, it is essential that oncologists are able to select the most appropriate therapies for men with metastatic castration resistant prostate cancer (mCRPC) in order to allow optimal treatment. Evidence indicates that cabazitaxel is active in mCRPC and is likely to be optimal therapy for those men with AR-V7 positive mCRPC cases. *(Cabazitaxel Remains Active in Patients Progressing After Docetaxel Followed by Novel Androgen Receptor Pathway Targeted Therapies. Al Nakouzi N. Eur Urol. 2014 May 2)*

There are no robust randomised trials to address the optimum sequencing of treatments for mCRPC. The meta-analysis of 10 published sequencing studies shows that overall survival is significantly better in patients with mCRPC who receive 3 agents (docetaxel, abiraterone and cabazitaxel) compared to those who receive 2 agents (docetaxel and abiraterone). *(Maines F et al. ASCO GU 2015 (abstract 258)*

Patients in STAMPEDE who are currently receiving early docetaxel as standard of care and enzalutamide/abiraterone as their trial option would have no further chemotherapy management option when they develop mCRPC. The ethics should be questioned around whether patients should consent to enter a trial now if they will have no management options or fewer treatment options in the future.

The views of British uro-oncologists are similar to the European and St Gallen consensus guidelines which advocate cabazitaxel as an option for mCRPC cases post-docetaxel. This is also reflected in the NCCN guidelines.

Finally, it is important to highlight that the role of cabazitaxel is different from that of radium-223 in the mCRPC setting and the benefits demonstrated for cabazitaxel are not limited to patients with bone metastases only.

Secretariat Address: bug@rightangleuk.com Web: www.bug.co.uk Alternatively, Prof Heather Payne heather_payne@blueyonder.co.uk
BUG is a registered charity Registered number 1116828 VAT number 919 3520 20

In summary, the British Uro-oncology Group requests a positive NICE appraisal allowing the prescribing of cabazitaxel for hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen. This would provide meaningful clinical benefit to men with mCRPC.

Yours faithfully

[redacted]

Royal College of Physicians
11 St Andrews Place
Regent's Park
London NW1 4LE
Tel: +44 (0)20 3075 1560

www.rcplondon.ac.uk

[redacted]

National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU

18 February 2016

Dear Mr Powell

Re: Cabazitaxel for treating hormone-relapsed metastatic prostate cancer after a docetaxel-containing regimen (review of TA255) [ID889] – Appraisal Consultation Document (ACD)

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 32,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-RCP-ACP-RCR are grateful for the opportunity to respond to the above consultation. The proposal to not recommend cabazitaxel appears to be based on health economic considerations rather than clinical effectiveness. Our clinical experts do not have the necessary expertise to comment on the health economic analyses. However, they feel strongly that cabazitaxel is an effective and well tolerated agent in the treatment of men with metastatic castration-resistant prostate cancer. It has become widely used throughout the world as a standard treatment and in the UK via the CDF.

Overall, we believe it would be highly regrettable if the drug were no longer to be available to UK patients. Both professional and patient groups would be extremely disappointed.

Yours sincerely

[redacted]

Response to the 'Appraisal consultation document Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen'

I am deeply disappointed by the provisional recommendations made in the Appraisal Consultation Document 'Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with a docetaxel-containing regimen'.

I was delaying my comments on this document until I had received a detailed response to a letter I have written to Sir Andrew Dillon after attending the STA meeting . In this letter I expressed my deep concern over the manner in which the meeting was conducted, particularly with reference to the treatment of my fellow Patient Representative and myself. However, to-date I have not received Sir Andrew's considered reply but felt that as the 22nd February was fast approaching it was important not to delay my response any longer.

The letter to Sir Andrew included a four-page 'paper' highlighting my concerns and detailing what I consider to be the shortcomings of the meeting together with some ideas for improvement. I feel that repeating these concerns in this response would be a breach of confidentially with regard to the correspondence I am having with Sir Andrew.

I will therefore restrict my comments to expressing my concern that I do not believe the process for the meeting was appropriately adhered to. I feel that the Chair paid only lip service to the need to involve Patient Representatives in the discussion process.

Apart from an invitation to make a very brief statement at the close of the meeting we were not encouraged or expected to enter the discussions at any point. Indeed, this is illustrated by a word count of the Appraisal Consultation Document. The whole document contains 12312 words, whilst the contribution from the two '*patient experts*' is expressed in 117 words; a clear indication of the credence given to our contribution.

We, the Patient Representatives, were not given any real opportunity to express the important part that Cabazitaxel plays in improving the quality of life, postponing death, and providing the consequential extension to family life.

It is heart-rending to witness the mental anguish, confusion and dismay men and their families suffer trying to obtain 'end-of-life' drugs, the availability of which are subject to the vagaries of processes such as this. These families are at a very vulnerable stage in their lives, or should I say deaths, and the stress, fatigue, pressure and turmoil this uncertainty places on them is cruel.

To write more would, I feel be fruitless, as it is apparent that the opinion and input of Patient Representatives and the many cancer suffers they represent, is of little value or importance to the decision making process. In consequence neither I, nor the charity I represent, the Prostate Cancer Support Organisation, can begin to support the provisional recommendations or consider them to have been arrived at following an adequate appraisal process.

Allan Higgin

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional - consultant oncologist caring for men with prostate cancer
Other role	consultant oncologist caring for men with prostate cancer
Organisation	
Location	England
Conflict	I do not work for sanofi or any other drug company .I recruit patients into clinical studies with cabazitaxel as with all of the drugs in prostate/ bladder or testicular cancer in my role as Chief Investigator, principal investigator , or research lead.I have experience of the pre 2005 era in prostate cancer before docetaxel and then the following 5 years in which we had no other effective second line treatment.
Notes	

Comments on individual sections of the ACD:

This document fails to acknowledge the heterogeneity of prostate cancer. There are compelling data that using a one sized fits all approach will neither benefit treatments nor utilise resource efficiently as patients will receive ineffective treatment in the absence of clinician choice .

There are multiple subtypes of prostate cancer on biopsies of which approx. 40% are thought to have mutations or specific gene expressions that confer resistance to androgen targeted agents. Small et al , Bova et al JAMA 2015) In particular Antonarakis (NEJM 2014, JAMA 2015)has demonstrated that Androgen receptor pathways with the variant AR7 receptor are relatively resistant to Androgen receptor targeted agents unlike taxane therapy. Watson et al (Nature Reviews Cancer Nov 2015) have highlighted the development of multiple factors in development of resistance to Androgen receptor targeted agents.

The use of abiraterone or enzalutamide in these men post docetaxel chemotherapy will therefore confer neither a survival nor symptomatic benefit and will waste resource , leaving this patient group with no treatment available other than best supportive care.

The use of palliative radiotherapy for symptoms of pain, visits to primary care and prescriptions for analgesia will thus increase and complications of advanced disease such as spinal cord compression and pathological fractures will place additional burdens on the NHS and social care.

Radium 223 is not indicated for men with incipient/occult very recently treated spinal cord compression, or for men with nodal disease greater than 2cm or those with visceral metastases. An entire patient group with effective disease is thus without second line therapy.

These men meet end of life criteria as they have no treatment options without the potential of second line chemotherapy

Cabazitaxel retains activity after androgen receptor targeted therapies (Pezaro et al European Urology 2014) unlike the ineffective sequencing of one androgen receptor targeted agents after another (Baimchini et al EJC 2013)

The UK 5 centre pooled data ECLIPSE (Real life treatment sequences and survival of men with mCRPC receiving cabazitaxel in UK clinical practice) (presented ESMO 2015, ESMO Asia 2015, Pan et al) has shown that 3 sequential treatments in patients with mCRPC offered survival gain over two sequential therapies. Single centre data from the Rosemere Cancer Centre (Pan et al 2015 ESMO ASIA) indicated that the Doc- Cab-Ab offered improved survival over Doc, Ab, Cab although in the pooled analysis for 5 centre in ECLIPSE, the survival results were very similar irrespective of which sequence was used. However, three sequential treatments offered significant gain.

Without clinician choice of appropriate therapy and with a simplistic one size actually fits none approach, the gains made in prostate cancer outcomes since 2005 will be lost as for 40% of our patient group there will be no effective second line options available, a position men with prostate cancer were in 10 years ago.

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	BAUN
Location	England
Conflict	no
Notes	

Comments on individual sections of the ACD:

This document does not acknowledge the heterogeneity of prostate cancer. Convincing evidence exists that using a one sized fits all approach neither benefits patients nor efficient use of resources, as patients will receive ineffective treatment in the absence of clinician choice .

There are multiple subtypes of prostate cancer on biopsies of which approximately 40% are thought to have mutations or specific gene expressions that confer resistance to androgen targeted agents. Small et al , Bova et al JAMA 2015) In particular Antonarakis (NEJM 2014, JAMA 2015)has demonstrated that Androgen receptor pathways with the variant AR7 receptor are relatively resistant to Androgen receptor targeted agents unlike taxane therapy. Watson et al (Nature Reviews Cancer Nov 2015) have highlighted the development of multiple factors in development of resistance to Androgen receptor targeted agents.

The use of abiraterone or enzalutamide in these men post docetaxel chemotherapy will therefore confer neither a survival nor symptomatic benefit and will waste resource , leaving this patient group with no treatment available other than best supportive care.

The use of palliative radiotherapy for symptoms of pain, visits to primary care and prescriptions for analgesia will thus increase and complications of advanced disease such as spinal cord compression and pathological fractures will place additional burdens on the NHS and social care.

Radium 223 is not indicated for men with incipient/occult very recently treated spinal cord compression, or for men with nodal disease greater than 2cm or those with

visceral metastases. An entire patient group with effective disease is thus without second line therapy.

These men meet end of life criteria as they have no treatment options without the potential of second line chemotherapy

Cabazitaxel retains activity after androgen receptor targeted therapies (Pezaro et al European Urology 2014) unlike the ineffective sequencing of one androgen receptor targeted agents after another (Baimchini et al EJC 2013)

The UK 5 centre pooled data ECLIPSE (Real life treatment sequences and survival of men with mCRPC receiving cabazitaxel in UK clinical practice) (presented ESMO 2015, ESMO Asia 2015, Pan et al) has shown that 3 sequential treatments in patients with mCRPC offered survival gain over two sequential therapies. Single centre data from the Rosemere Cancer Centre (Pan et al 2015 ESMO ASIA) indicated that the Doc- Cab-Ab offered improved survival over Doc, Ab, Cab although in the pooled analysis for 5 centre in ECLIPSE, the survival results were very similar irrespective of which sequence was used. However, three sequential treatments offered significant gain.

Without clinician choice of appropriate therapy and with a simplistic one size fits all approach, the gains made in prostate cancer outcomes since 2005 will be lost as for 40% of our patient group there will be no effective second line options available, a position men with prostate cancer were in 10 years ago.

Name	[redacted]
Role	Patient
Other role	Ex-Chairman, Bay Prostate Ca. Support Group, Lancaster
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
I am very concerned that at present you are not minded to approve cabazitaxel for use in the NHS. This drug offers a valuable second-line chemotherapy for advanced prostate Ca. patients where all else has failed, and has been shown to extend life and improve quality of life, factors highly valued by patients as they reach the end of life. Failure to approve cabazitaxel removes all hope and discriminates against men who have nowhere else to turn. I urge you to reverse your interim decision.	

Name	[redacted]
Role	NHS Professional
Other role	Consultant Clinical Oncologist
Organisation	
Location	Wales
Conflict	I have been paid honoraria by Sanofi in the past .
Notes	
Comments on individual sections of the ACD:	

There are a proportion of patients with metastatic hormone refractory prostate cancer who do not respond durably to initial hormone treatment. After docetaxel chemotherapy, these patients have the NICE approved options of enzalutamide or abiraterone availabel to them. Neither of these agents is effective in patients who have had a poor response to first line androgen deprivation. Cabazitaxel is well tolerated, and would be a useful option for these patients.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Clinical oncologist
Organisation	Clatterbridge Cancer Centre submitted on behalf of following uro-oncologists: [redacted]
Location	England
Conflict	selected expert for appraisal Jan 2016 Investigator on studies with agent. Unrelated funding for studies outside CRPC
Notes	

Comments on individual sections of the ACD:

Dear Colleague

RE: ACD TAG 255 1st February 2016.

We write to express our disappointment and concerns regarding the recent ACD on cabazitaxel and note that:

˜Cabazitaxel does not provide enough benefit to patients to justify its high cost even when the special considerations were applied, so NICE did not recommend it.™

We were involved with the original TROPIC trial and the subsequent EAP programme. Since then we have prescribed this medicine to numerous patients and have found it to be effective in both offering life extension and also palliative benefit to a number of patients.

Removing this medicine would constrain our ability to treat patients efficiently. Moreover the greatest impact will be on patients who have aggressive prostate cancer that has responded poorly to LHRH analogue therapy or indeed docetaxel treatment. These patients are unlikely to respond to enzalutamide or abiraterone treatment.

Cabazitaxel has Level 1 efficacy evidence; indeed most of the patients entering the TROPIC Phase III study had docetaxel resistant disease and/or progression in 70% within 3 months. Therefore they were a group of patients with a very poor prognosis.

We therefore ask you to reconsider the scientific evidence for this medicine and review your decision in a patient sub group that clearly has an unmet need.

Kind regards

Yours sincerely

[redacted]

Name	[redacted]
Role	NHS Professional
Other role	[redacted]: Royal Marsden Hospital
Organisation	Royal Marsden NHS Trust
Location	England
Conflict	
Notes	I have received speaker and travel fees from Sanofi

Comments on individual sections of the ACD:

Thank you for providing the opportunity to respond to the Cabazitaxel ACD.

Cabazitaxel is a drug which provides a unique role in the treatment of prostate cancer. It has demonstrated an unequivocal overall survival advantage in patients who have progressed after Docetaxel chemotherapy. The great majority of patients will now have had either Abiraterone or Enzalutamide prior to receiving or after Docetaxel chemotherapy. A significant proportion remain, fit and enjoy a reasonable quality of life despite progressive disease. In this cohort of patients who have had Abiraterone/Enzalutamide and progressed after Docetaxel, Cabazitaxel is the only effective treatment option (for patients with bone only disease, Alpharadin could be considered but a significant majority of patients have bone and soft tissue disease).

The difficulty in assessing evidence in this setting (as in many cases) is that the main data supporting Cabazitaxel comes from a study which pre-dates the use of both Abiraterone and Enzalutamide. In clinical practice, in our large academic institution, the great majority of patients in whom we use Cabazitaxel would have already had either Abiraterone or Enzalutamide, either pre or prior to Docetaxel. It is not currently clear from the clinical evidence what the best sequencing for these drug are. In routine clinical practice around the country, it does vary as to who provides Docetaxel and who provides Abiraterone or Enzalutamide first. In our practice, we find Cabazitaxel to be effective in castrate resistant post-Docetaxel setting irrespective of whether the patients have had Docetaxel pre or post Enzalutamide/Abi. I note the comments on Cabazitaxel being extendedly dominated by Enzalutamide but no reference to Abiraterone in the setting?

There appears to be significant emerging data about resistance to both Abiraterone and Enzalutamide. In this cohort of patients (a poor prognosis group) there seems to be a clear advantage to have two chemotherapy drugs of both which have shown a survival advantage. Although not yet tested in clinical trials, there are a number of trials and development to test Cabazitaxel in the setting, as it is our clinical experience that it is effective where both Abiraterone and Enzalutamide resistance is present.

With the use of Docetaxel in the hormone sensitive setting (based on Stampede trial data), there will be a general shift in practice as to when Docetaxel is used. It will result in Docetaxel being used prior to Abiraterone or Enzalutamide in the hormone sensitive setting. In my view, this would wrongly potentially preclude the use of

Cabazitaxel later in the disease process, as patients would not have had Abiraterone or Enzalutamide œprior to Docetaxel. I would encourage NICE to negotiate with the company to consider reducing the cost of the drug to bring it below the required QALY as the loss Cabazitaxel would be disadvantageous to our patients who currently have the benefit of the treatment with a clear survival advantage.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
My husband was on cabazitaxel last year and had no side effects. It enabled us to carry out a full and active life whilst under going the treatment and increased his life expectancy. Please do not discontinue the availability of this drug - it would be a great loss to prostate sufferers.	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Cabazitaxel is the reason I'm alive today and able to write this. It was the one form of chemotherapy that had a dramatic and positive effect on my prostate cancer - with few side-effects - after other treatments had failed. It must remain available for the thousands of other sufferers in my situation. Please!	

ERG comments on Sanofi's response to the ACD.

In their response to the ACD Sanofi supplied an updated economic model. Compared with the model previously submitted by Sanofi, this model had the following changes:

- A new patient-access scheme (PAS) price for cabazitaxel.
- Piecewise curve fit for the cabazitaxel arm, with the change in curves at 2.1 months.
- Use of e-MIT prices in preference to BNF prices where applicable.
- Country specific treatment mix for people who progress whilst receiving cabazitaxel or one of its comparators.
- Discontinuation for reasons other than disease progression not modelled.
- No reduced utility in the last three months of life.
- Drug wastage modelled for mitoxantrone (but not for cabazitaxel).

The ERG has checked the implementation of these changes. It has also checked that using the previous PAS price for cabazitaxel led to the cost-effectiveness results presented by Sanofi during the FACT check. The following points were identified:

1. There are e-MIT prices available for prednisolone & co-codamol, but these have not been included in the model. Including these prices has a minimal impact on the ICER, reducing it from £45,159 to £45,151 (a reduction of 0.02%).
2. The implementation of piecewise curves is hard-coded. However, the Kaplan-Meier data and Weibull parameters used are presented. From this information the ERG was able to replicate the company's approach. The ERG notes that the approach used requires that, for events occurring after 2.1 months, the analysis time starts at 2.1 months. This is not explicitly mentioned in the company's submission.

The ERG notes that if drug wastage is modelled for cabazitaxel, the ICER increases to above [redacted] (value: [redacted]).

From: Qualie Malcolm (NHS ENGLAND)
Sent: Wednesday, February 17, 2016 6:28 AM
To: Hingle, Andrew PH/GB
Cc: Rycroft, Tom PH/GB;
Subject: cabazitaxel

Andrew,

Thank you for sharing your plans regarding a potential pricing structure for cabazitaxel in prostate cancer which includes a PAS.

I can confirm the cabazitaxel per mg drug supply service as described by Sanofi is both implementable across NHS England Trusts and will guarantee the removal of all drug wastage costs from the conversion of vials to dose specific patient infusion bags.

Specific areas which might cause issues have been managed through the design of the service: ensuring validated wastage of compounded bags is covered for justified patient non-attendance or inability to receive dose, provision for multiple compounding vendors and for individual Trust pharmacy departments to act as vendors within the service should they not wish to engage a third party manufacturer. Some Trusts may have to organise blood tests to be carried out two days prior to the scheduled day of chemotherapy administration to ensure cell counts are sufficient for the patient to receive cabazitaxel, but this is not inconsistent with the trend towards more efficient chemotherapy services for patients in the NHS.

The proposed service could be improved through the use of dose-banded infusion bags as consistent with the current NHS England chemotherapy initiative and quality assurance of longer shelf-life of such dose banded infusion bags. This would enable significant IV chemotherapy service efficiencies. However, such provisions would require robust validation data which I understand is not currently available or appropriate for the manufacturer to adopt within the service, as it is not consistent with the existing cabazitaxel marketing authorisation.

Regards

Malcolm

Malcolm Qualie
Pharmacy Lead
Specialised Services
NHS England

Tele no: [redacted]
Email address: [redacted]
PA: [redacted]
Tele no: [redacted]
Email address: xxxxxxxxxxxxxxxxx