CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

abiraterone, prednisone and docetaxel

Indication: metastatic castration sensitive prostate cancer (mCSPC).

August 3, 2023

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PX0298
Name of the drug and Indication(s)	abiraterone, prednisone, docetaxel for metastatic castration sensitive prostate cancer (mCSPC)
Organization Providing Feedback	PAG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
3. Please specify questions or issues that should be addressed by CAPCA. (oncology only)
1. 2.
Support strategy
4. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc. The algorithm will need to be updated

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PX0298
Brand name (generic)	Abiraterone Acetate and Prednisone/Dexamethasone with Docetaxel
Indication(s)/ Reimbursement Request	Abiraterone acetate and prednisone or dexamethasone for the treatment of adults with metastatic castration-sensitive prostate cancer (mCSPC) in combination with docetaxel and androgen deprivation therapy (ADT)
Organization	Janssen Inc.
Contact information[a]	Name: Bonnie Kam

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

The evidence from the PEACE-1 study does not support a recommendation for the entire population within the reimbursement question (Draft Recommendation, Fig. 1). In addition, PEACE-1 was not designed with regulatory rigor for filing, and has not yet been reviewed nor approved by Health Canada. There was also no monitoring or inspection for adequacy of safety reporting, which is a key aspect to the decision to implement this triplet therapy. As such, the certainty in the evidence is limited. Therefore, **Janssen Inc. requests that the recommendation be changed to include reimbursement conditions based on the following:**

i) ***De novo* vs. metachronous mCSPC** (Draft Recommendation, Table 1, Decision Nodes B & D)
PEACE-1 only enrolled patients with *de novo* mCSPC, the effectiveness of abiraterone + ADT + docetaxel in metachronous mCSPC has not been demonstrated by either direct or indirect evidence. CADTH's FMEC also noted that the PEACE-1 trial demonstrated clinical benefit in patients with *de novo* mCSPC (Table 1, Node B). In addition, in the update to the American Society for Clinical Oncology (ASCO) guideline on the management of non-castrate advanced prostate cancer, ADT + abiraterone + docetaxel is recommended to be offered only to mCPSC patients with *de novo* and high-volume disease.[1,2] Therefore, the extrapolation of safety/efficacy of this triplet therapy to metachronous disease is unwarranted and creates substantial uncertainty.

ii) **High-volume disease** (Draft Recommendation, Table 1, Decision Node B & D)
The PEACE-1 trial showed that both overall survival (OS) and radiographic progression-free survival (rPFS) benefits were largely confined to patients with high-volume disease. The confidence intervals (CIs) of the hazard ratios (HRs) for both OS and rPFS crossed 1 in the subgroup of patients with low-volume disease suggesting uncertainty as these patients may not benefit from the triplet therapy and are subjected to the unnecessary increased toxicity and the associated detriment to quality of life (QoL) with docetaxel therapy.[3,4] This was also highlighted by the Clinical Expert: "There is currently a gap in both the direct and indirect evidence regarding the efficacy of triplet therapy with abiraterone plus docetaxel plus ADT vs. doublet therapy with apalutamide plus ADT or enzalutamide plus ADT." (Draft Clinical Review Report, Table 5, p.21 of 85)

Docetaxel is one of the most widely used cytotoxic agents for solid malignancies. However, it is associated with substantial toxicities, including leukopenia and neutropenia, anemia, alopecia, nausea, diarrhea, fatigue, as well as neurotoxicity and nail disorders, all of which negatively impact patients QoL[3,4], and may require additional resources for managing toxicity (e.g., G-CSF prophylaxis).[5] Therefore, docetaxel-based regimen should be limited to those patients with more severe disease as well as those who are fit and willing to receive docetaxel.

In the most recent update to the Canadian Urological Association (CUA) treatment algorithm for mCSPC, ADT + abiraterone + docetaxel is recommended only for mCPSC patients with high-volume/high-risk disease* who are able to tolerate docetaxel.[6] Similarly, as noted above, the ASCO guideline only supports the use of ADT + abiraterone + docetaxel in mCPSC patients with high-volume disease and *de novo* cancer.[1,2] For low-volume disease, both guidelines maintain the use of single-agents or doublet therapies.[1,2,6] Consistent with these guidelines, the clinical expert consulted by CADTH also "did not endorse use of triplet therapy for all men with mCSPC." (Draft Clinical Review Report, *External Validity*, p.58 of 85) The uncertainty in benefit of this triplet regimen in low-volume disease is also recognized by the CADTH reviewers: "…recruitment of patients who, while fit to receive docetaxel, may not be expected to benefit from treatment according to current guidelines (e.g., low-volume and/or low-risk disease)." (Draft Clinical Review Report, *Critical Appraisal,* p.12 of 85; *External Validity*, p.58 of 85)

* Defined by the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis; low-volume is defined as all other metastatic castration-naive and castration-sensitive prostate cancer.

iii) **ECOG** (Draft Recommendation, Table 1, Decision Node B & D).
PEACE-1 only enrolled patients with ECOG 0 to 1 or 2 if due to bone pain; consequently, no data exists to support the generalization of the results from PEACE-1 to mCPSC patients with worse performance status. The clinical expert highlighted that for those with worse status, "cautious use of ARPI plus ADT is preferred" and does not agree with generalization of the results to those with worse performance status (Draft Clinical Review Report, Table 5, Considerations for initiation of therapy, p.22 of 85). In the absence of clinical data (direct or indirect) and absence of support from the clinical expert, the results of the PEACE-1 trial in patients with ECOG 0 to 1 or 2 if due to bone pain should not be extrapolated to those with worse ECOG performance status.

iv) **Fitness to receive docetaxel** (Draft Recommendation, Table 1, Decision Node B & D)
PEACE-1 only enrolled patients who are deemed fit to receive docetaxel; no data exists to support the generalization of the results from PEACE-1 to mCPSC patients with that are deemed unsuited to receive docetaxel. This view is supported by clinical expert consulted by CADTH highlighting that "triplet therapy with abiraterone with prednisone…plus docetaxel plus ADT may be considered for younger patients who are both well-informed and in better health, but have higher risk disease features (e.g., critical organ involvement, high volume disease, high risk disease) and/or who may prefer more aggressive therapy… Patients who are not chemo fit (e.g., due to comorbidities) or have contraindications to abiraterone would be least suitable for this triplet regimen." (Draft Clinical Review Report, *Input from a Clinical Expert Consulted by CADTH*, p.7 of 85) Considering the docetaxel-related toxicity discussed in ii) above, docetaxel-based regimen is unsuitable for those who are unfit and should be limited to those patients who are fit and willing to receive docetaxel.

v) Per CADTH's Clinical Review guideline (section 4.1) in the *Non-Sponsored Reimbursement Review Procedures*, review is based on "the most relevant clinical information", even when reflecting input from clinician groups.[7] Consequently, the extrapolation of data to another patient population (i.e., from *de novo* to metachronous, from those fit to receive docetaxel to those all mCSPC, and from ECOG 0-1 or 2 if due to bone pain to ≥2) for which there is no relevant clinical information (in the form direct or indirect evidence) not only does not support a recommendation for the entire population within the reimbursement question as laid out by the Decision Path within the Deliberative Framework (Fig. 1), it also contradicts the guideline as put forth by CADTH.

vi) There was no input from clinician groups received for this review and expert input was provided by a single clinical expert, it is therefore uncertain whether differences in interpretation of the data would exist based on jurisdiction experience and practice patterns. Similarly, the implementation issues identified by the PAG (Draft Clinical Review Report, Table 5) may also be better served if, in the future, clinical experts from more than one CADTH-participating jurisdictions provide input.

Therefore, Janssen Inc. requests that the recommendation be changed to include the reimbursement conditions with the following initiation criteria:

1. Abiraterone plus ADT should be reimbursed in combination with prednisone in patients with mCSPC with the following criteria:
   1.1. Diagnosed with *de novo* disease
   1.2. Presents with high-volume disease
   1.3. Clinically fit and willing to receive docetaxel
   1.4. With ECOG performance status of 0 to 1 or 2 if due to bone pain

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

Although the issues identified by Janssen in the Industry Input are presented in the Review Report, it is unclear how those inputs were considered. No clear evidence was provided to support CADTH's deliberation and extrapolation of results to patient populations beyond those evaluated in PEACE-1.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

N/A

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

The PAG sought clarification as to whether patients on active treatment may have a time-limited opportunity to switch to the triplet therapy. The clinical expert indicated the following (Draft Clinical Review Report, Table 5, p.23 of 85): "Patients who recently initiated docetaxel plus ADT should be eligible to add on abiraterone within a period of approximately 6 months following treatment initiation to allow overlap with the policy change (i.e., if the triplet therapy is funded). However, after a reasonable time has elapsed from policy implementation, this time frame should align with the clinical trial (i.e., abiraterone should be initiated with 3 months of starting treatment with docetaxel plus ADT)." ***Janssen response*:** There is no evidence to support the initiation of abiraterone 6 months following the start of docetaxel plus ADT. In addition, please note the correct timeframe from the PEACE-1 trial which states that "Patients assigned to receive abiraterone received 1000 mg of abiraterone (four 250 mg tablets, orally) once daily plus prednisone 5 mg orally twice daily, starting within 6 weeks after ADT initiation." Consequently, the impact of delaying the addition of abiraterone to docetaxel and ADT beyond the trial-specified timeframe is unknown.

It was also noted that "Patients who are currently receiving one of apalutamide or enzalutamide or abiraterone plus ADT should be allowed to switch to the triplet if funding is implemented. This decision would be based on patient preference and clinician discretion but should be made within a restricted time frame (e.g., approximately 4 to 6 months)." ***Janssen response:*** PEACE-1 was not designed to test whether adding docetaxel to an androgen receptor-axis-targeted therapies (ARAT) + ADT was more efficacious than ARAT + ADT alone. In addition, no other studies were conducted to demonstrate a benefit of switching from apalutamide or enzalutamide-based doublet to triplet therapies. Therefore, based on lack of evidence, Janssen does not support the switch of patients currently receiving one of apalutamide or enzalutamide-based doublet or abiraterone + ADT, and whose disease is well-controlled, to triplet therapy.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

Please refer to section 1 above.

[a] CADTH may contact this person if comments require clarification.

References

1. Tanzola M. Triplet Therapy Trials Prompt Focused Update to ASCO Guideline on Management of Noncastrate Advanced Prostate Cancer. 2023; https://dailynews.ascopubs.org/do/triplet-therapy-trials-prompt-focused-update-asco-guideline-management-noncastrate. Accessed July 25, 2023.
2. Virgo KS, Rumble RB, Talcott J. Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update. *J Clin Oncol.* 2023;41(20):3652-3656.
3. Al-Batran SE, Hozaeel W, Tauchert FK, et al. The impact of docetaxel-related toxicities on health-related quality of life in patients with metastatic cancer (QoliTax). *Ann Oncol.* 2015;26(6):1244-1248.
4. Eckhoff L, Knoop A, Jensen MB, Ewertz M. Persistence of docetaxel-induced neuropathy and impact on quality of life among breast cancer survivors. *Eur J Cancer.* 2015;51(3):292-300.
5. Cancer Care Ontario. Drug Monograph. DOCEtaxel. CCO Formulary - April 2023.
6. Chi KN, Hotte S, Niazi T, et al. CUA Tool Card & Treatment Algorithm for the Treatment of Metastatic Castration-Sensitive Prostate Cancer (mCSPC). Canadian Urological Association; 2023.
7. CADTH. Non-Sponsored Reimbursement Review Procedures. June 2023.