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TRANSPARENCY COMMITTEE

OPINION

17 October 2012

The draft Opinion adopted by the Transparency Committee on 3 October 2012 was examined at a hearing on 17 October 2012

JEVTANA 60 mg, concentrate and solvent for solution for infusion
Box with 1 vial of concentrate and 1 vial of solvent (CIP code: 579 849-7)

Applicant: SANOFI-AVENTIS FRANCE

Cabazitaxel

List I
Reserved for hospital use
Prescription restricted to oncology or haematology specialists or doctors with cancer training. Medicine requiring special monitoring during treatment.

Approved for use by hospitals and various public services (Official Gazette of 27 March 2012).

Date of Marketing Authorisation (centralised procedure): 17 March 2011

Reason for request: Re-assessment of the Improvement in Actual Benefit following submission of new data, on the initiative of the applicant, in accordance with Article L. 163-12 of the French Social Security Code.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Cabazitaxel

1.2. Indication

"JEVTANA, in combination with prednisone or prednisolone, is indicated in the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen."

1.3. Dosage

"The recommended dose of JEVTANA is 25 mg/m^2 administered as a 1 hour intravenous infusion every 3 weeks in combination with oral prednisone or prednisolone 10 mg administered daily throughout treatment."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01C	Plant alkaloids and other natural products
L01CD	Taxanes
L01CD04	Cabazitaxel

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines:

None.

2.3. Medicines with a similar therapeutic aim

- ZYTIGA (abiraterone acetate)

Substantial actual benefit and level III improvement in actual benefit in terms of efficacy and safety in the treatment of metastatic castration-resistant prostate cancer which has progressed on or after a docetaxel-based chemotherapy regimen (TC Opinion of 29/02/2012)

- NOVANTRONE (mitoxantrone)
- TAXOTERE (docetaxel)
- ESTRACYT (estramustine)

3 ANALYSIS OF AVAILABLE DATA

On 19 October 2011, the Transparency Committee approved the inclusion of JEVTANA on the list of medicines approved for use by hospitals. In this opinion, the Transparency Committee stated that JEVTANA had a substantial actual benefit (AB) and a level IV improvement in actual benefit (IAB) in the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.
Since then, on 29 February 2012, the Transparency Committee approved the inclusion of an alternative to JEVTANA, ZYTIGA (abiraterone acetate), on the list of medicines reimbursed by National Insurance and approved for use by hospitals. ZYTIGA, administered orally, has a substantial AB and a level III IAB in terms of efficacy and safety in the treatment of metastatic castration-resistant prostate cancer which has progressed on or after treatment with docetaxel.
The applicant has requested a re-evaluation of the IAB for its proprietary medicinal product JEVTANA.

The dossier requesting re-evaluation of the IAB comprises:

- results from a sub-group analysis of a pivotal study (TROPIC) that has already been examined by the Committee. These sub-groups mainly include patients who stopped treatment with docetaxel due to disease progression,

- safety data from temporary use authorisations for a named patient (nominative TUA) or a cohort (cohort TUA) granted in France between 16 December 2010 and 6 July 2011,

- interim results from three observational studies, currently in progress, investigating the safety of cabazitaxel in real conditions of use,

- data from two observational studies from the literature concerning abiraterone acetate (ZYTIGA). Given the absence of comparative data versus JEVTANA, this information will not be taken into consideration.

3.1. Efficacy and safety

A/ Reminder of the efficacy and safety data evaluated by the TC (Opinion of 19 October 2011)

Efficacy and safety data for JEVTANA in the indication for metastatic prostate cancer are taken from an open-label, randomised phase III study[1] comparing cabazitaxel (JEVTANA) to mitoxantrone, both of which were combined with prednisone or prednisolone, in 755 patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-based regimen.
The median age of patients was 68 years in the cabazitaxel group and 67 years in the mitoxantrone group. Over 90% of patients had an ECOG performance score of 0 or 1.
The majority of the patients included in the study had received a single line of docetaxel-containing chemotherapy (84% in the cabazitaxel group and 87% in the mitoxantrone group).

The median overall survival (primary efficacy endpoint) was 15.1 months in the cabazitaxel group versus 12.7 months in the mitoxantrone group, i.e. an absolute difference of 2.4 months in favour of the cabazitaxel group (HR = 0.70, 95% CI: [0.59 - 0.83])

The median progression-free survival was 2.8 months in the cabazitaxel group versus 1.4 months in the mitoxantrone group, i.e. a difference of 1.4 months in favour of cabazitaxel (HR = 0.74, 95% CI: [0.64 - 0.86]).

[1] de Bono J. S. et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010; 376: 1147–54.

The biological response (decrease of PSA level greater than or equal to 50%) was 39.2% in the cabazitaxel group versus 17.8% in the mitoxantrone group, p = 0.0002.
The sub-group analysis taking prognostic factors into account suggests a heterogeneous effect on overall survival, in particular a lack of difference between cabazitaxel and mitoxantrone in patients receiving three cycles or fewer (225 mg/m^2) of docetaxel.
There was no difference in response rate between the two groups in terms of pain and the median time to pain progression.
No quality of life data are available.
Safety was not as good in the cabazitaxel group as in the mitoxantrone group. Specifically, the following were more common in the cabazitaxel group: discontinuation of treatment due to adverse events (18.3% versus 8.4%) and grade ≥ 3 adverse events (57.4% versus 39.4%) including neutropenia (21.3% versus 7%), diarrhoea (6.2% versus 0.3%) and asthenia (4.6% versus 2.4%).

In addition, in April 2011 the applicant launched a study (EFC11785)[2] in patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. The aim of this phase III study, which is still currently recruiting patients, is to demonstrate non-inferiority in terms of overall survival of a cabazitaxel dose of 20 mg/m^2 versus 25 mg/m^2 in combination with prednisone.
In view of the high risk of the onset of serious adverse events found with a cabazitaxel dose of 25 mg/m^2 in the pivotal study, and in anticipation of the results from this non-inferiority study, the optimum cabazitaxel dosage remains to be defined.

B/ Data submitted in the re-evaluation dossier

New clinical study:

No new studies have been carried out with JEVTANA since the last Transparency Committee Opinion of 19 October 2011.

Sub-group analysis of the TROPIC study

The applicant has submitted results from a sub-group analysis of the pivotal study (TROPIC). This analysis is based on the overall survival and safety in the sub-groups of patients who stopped treatment with docetaxel due to disease progression. From these results, the following points are raised:
- in the sub-group of patients who stopped docetaxel due to disease progression (62%), the results indicate a median increase in overall survival of 2.9 months [HR = 0.70; 95% CI 0.57 – 0.87] in favour of cabazitaxel compared with mitoxantrone,
- in the sub-group of patients who had stopped treatment with docetaxel due to disease progression and had a histologically poorly differentiated tumour (Gleason score 7 to 10), the median increase in overall survival was 4.1 months in favour of cabazitaxel compared with mitoxantrone [HR = 0.65; 95% CI 0.50 – 0.87],
- the safety profile in the sub-population of patients who stopped treatment with docetaxel due to disease progression was similar to that found in the total population of the cabazitaxel group in the pivotal study.

Safety data from temporary use authorisations for a named patient (nominative TUA) or cohort (cohort TUA) granted in France

The report of TUA data covering the period from 20/12/2010 to 06/07/2011 was written based on follow-up forms as specified in the therapeutic use protocol.
As of 06 July 2011, 184 patients had been treated with JEVTANA: 61 patients within the scope of a named-patient temporary use authorisation (nominative TUA) and 123 patients treated within the scope of a temporary use authorisation for a cohort (cohort TUA).
All patients had hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen (9% of patients received more than one line of docetaxel-based chemotherapy).

[2] http://clinicaltrials.gov/show/NCT01308580

The median age of patients was 67.2 years and 38% were over 70 years old. For 85% of patients, their ECOG (Eastern Cooperative Oncology Group representing performance status) score was between 0 and 1.

Disease progression before starting treatment was primarily marked by an increase of PSA levels in 92% of patients, by the occurrence of bone metastases in 77% of patients and by clinical progression with a worsening in symptoms or pain in 71% of patients.
The median interval between the last line of chemotherapy and administration of JEVTANA was 4 months.
Follow-up data was analysed based on 240 follow-up forms, including:
- 86 no. 1 follow-up forms,
- 50 no. 2 follow-up forms,
- 31 no. 3 follow-up forms,
- 17 no. 4 follow-up forms,
- 10 no. 5 follow-up forms,
- 5 no. 6 follow-up forms,
- 41 discontinuation forms

As follow-up forms were not collected for each cycle, the number of cycles of chemotherapy received by each patient is known for only 47 of the 184 patients (25%) who received, on average, 3.8 cycles of JEVTANA.

A total of 41 treatment discontinuation forms were received, after an average of 4 cycles. Treatment was discontinued due to disease progression in 44% of cases, due to a serious or non-serious adverse effect in 17% of cases and due to a non-toxic related death in 15% of cases.
During the TUA period, 25 of the 184 patients treated under the TUA had at least one serious adverse event and 59 had at least one non-serious adverse event.
The 25 serious cases corresponded to 61 serious adverse events, while the 59 non-serious cases corresponded to 202 non-serious adverse events.

Among the serious adverse events reported, the most common were haematological (32.79%, including 9.54% of febrile neutropenia) or gastric (14.75%, including 9.84% episodes of diarrhoea). The effects had a favourable outcome after several days of treatment with G-CSF for febrile neutropenia, and loperamide and rehydration therapy for diarrhoea.

For nine patients, the outcome was fatal, with progression of the cancer for seven of them. For the other two, death was linked to respiratory distress as the result of aspiration pneumonia for one patient who apparently had problems swallowing, although there are no other details, and due to chronic respiratory failure for one patient with a previous history of lung cancer with a right pneumonectomy.

A total of six unexpected serious cases were reported during the TUA period, including two linked to cabazitaxel. These were a case of acute tubular necrosis secondary to septic shock with febrile neutropenia and a pulmonary embolism.

Due to the limited number of forms collected and the absence of information on the number of treatment cycles received for 75% of patients, no definitive conclusions can be drawn from the data from these TUA periods.

<u>PSUR data:</u>
Analysis of the two PSURs covering the period from 17 December 2010 to 16 December 2011 did not identify any specific signals and did not lead to any amendments being made to the SPC since the last Transparency Committee opinion.

Safety data from observational studies

Observational studies evaluating the safety of cabazitaxel under real conditions of use were instigated in Italy, the United Kingdom and Germany. Data from these studies are only available in the form of abstracts and without any final analysis. As there are no study reports or final analyses available, these data do not allow any conclusions to be drawn regarding the safety of cabazitaxel. These studies are therefore only cited for information purposes.

- **Italy**[3]

Methodology

A non-comparative observational study carried out in patients with hormone refractory metastatic prostate cancer, previously treated with docetaxel and receiving 25 mg/m^2 of cabazitaxel in a 3 week cycle. The aim of this study was to gather safety data under real conditions of use.

Results

At the time of the interim analysis, 90 of the 232 patients (39%) required had been enrolled.
The median age of patients was 70 years, 97.8% of them had an ECOG at least equal to 1 and 86.7% had bone metastases.
The median number of cycles of cabazitaxel received was four.
More than a third of patients (37%) stopped treatment prematurely due to disease progression.
The most common adverse effects of grade ≥ 3 were febrile neutropenia (3.3%), diarrhoea (1.1%) and asthenia (3.3%).

- **United Kingdom**[4]

Methodology

A non-comparative observational study carried out in patients with hormone-refractory metastatic prostate cancer, previously treated with a docetaxel-based treatment and receiving 25 mg/m^2 of cabazitaxel in a 3-week cycle. The aim of this study was to gather quality of life and safety data under real conditions of use.
A safety evaluation was carried out at the start of each cycle. Patients completed the EQ-5D quality of life questionnaire and a visual analogue scale for pain at the start of the treatment cycle, for one cycle out of every two completed.

Results

At the time of the interim analysis, 62 patients had been enrolled. However, the number of patients required for the final analysis is not known.
The median age was 68 years, with 24% of patients being older than 75 years.
The median number of cycles received was three. For one patient, a cycle had to be postponed and for two patients, the dose had to be reduced.
At the time of this analysis, 83% of patients were in the process of being treated. Prophylactic treatment with GCS-F was given to 85% of patients from the first treatment cycle. Discontinuation of treatment was noted for seven patients, including five due to disease progression.
Safety was evaluated in 41 patients. The most common adverse effects of grade ≥ 3 were neutropenia with sepsis (4.9%) and diarrhoea (2.4%).
The percentage of patients not reporting any pain was 22.6% at inclusion, 38% at cycle 2 and 50% at cycle 4.

[3] Bracarda S.et al. Preliminary safety results of an Italian early-access program (EAP) with cabazitaxel plus prednisone (CbzP) in patients with docetaxel-refractory metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2012; 30 (suppl 5) abstr 253.
[4] Bahl A.K. et al. Cabazitaxel for metastatic castration resistant prostate cancer (mCRPC). Interim safety and quality of life (QOL) data from the UK early access programme. Abstract 129. EAU 2012

- **Germany**[5]

Methodology
A non-comparative observational study carried out in patients with hormone refractory metastatic prostate cancer who failed docetaxel-based chemotherapy and receiving 25 mg/m^2 of cabazitaxel in a 3-week cycle. The aim of this study was to gather safety data under real conditions of use.

Results
At the time of the interim analysis, 111 patients had been enrolled. However, the number of patients required for the final analysis is not known.
The median age of patients was 68 years, with 18% of patients being older than 75.
Approximately three-quarters (78.7%) of patients had progressed during treatment with docetaxel or in the 6 months following the last docetaxel dose.
Thirty-one percent of patients presented with adverse effects that were grade ≥ 3. Grade ≥3 adverse effects said to be the "most significant" were: febrile neutropenia 3.6% and diarrhoea 0.9%.

3.2. Conclusion

JEVTANA (cabazitaxel) obtained Marketing Authorisation through the centralised procedure on 17 March 2011 for the indication "in combination with prednisone or prednisolone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen".
On 19 October 2011, the Transparency Committee approved the inclusion of JEVTANA on the list of medicines approved for use by hospitals. In this opinion, The Transparency Committee stated that JEVTANA had a substantial AB and a level IV IAB for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. This decision was based on the results from the randomised, open-label TROPIC pivotal study, versus mitoxantrone, which demonstrated an absolute increase in median overall survival (primary endpoint) of 2.4 months in favour of the cabazitaxel group.
As JEVTANA was not able to be included on the list of medicines approved for reimbursement in addition to hospital use, the applicant has requested a re-evaluation of the IAB for this proprietary medicinal product.
Data considered were:

- results from the sub-group analysis of the pivotal study (TROPIC) specifically concerning the sub-population of patients for whom docetaxel was stopped due to disease progression,
- safety data from temporary use authorisations for a named patient (nominative TUA) or cohort (cohort TUA) granted in France between 16 December 2010 and 6 July 2011
- interim results from three observational studies, still in progress, based on the safety of cabazitaxel under real conditions of use.

In view of:

- the demonstrated efficacy of JEVTANA in terms of overall survival (primary endpoint) of 15.1 months, versus mitoxantrone (considered a relevant comparator), in a final analysis of the TROPIC pivotal study,
- the results from a sub-group analysis carried out on the TROPIC study (patients who had stopped docetaxel due to progression),
- the demonstrated efficacy of ZYTIGA in terms of overall survival (primary endpoint) of 14.8 months, versus placebo, in an interim analysis specified in the protocol of the pivotal study COU-AA-301,
- the safety results from the TUA data but the limited number of forms collected during the temporary use authorisation periods (TUA) and the absence of information on the number of

[5] Heidenreich et al. Cabazitaxel plus prednisone for patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing regimen: Interim analysis on treatment associated side effects resulting from a compassionate-use programme (CUP). Abstract 128. EAU 2012

JEVTANA treatment cycles received for 75% of patients on a temporary use authorisation (TUA),
- the data from the three observational safety studies, available only as abstracts and without any final analyses,
- the evaluation of the therapeutic benefit of JEVTANA should be modified relative to the evaluation carried out in 2011.

Since the previous TC opinion of 19 October 2011, the therapeutic strategy has seen significant developments related to the introduction of abiraterone acetate (ZYTIGA) to the list of approved treatments for patients with hormone-refractory metastatic prostate cancer previously treated with docetaxel-based chemotherapy.
Taking into account the initial resistance data for hormone therapy with abiraterone observed for approximately one third of patients who have failed treatment with docetaxel[6]and all of the data noted above, the Committee estimates that the therapeutic benefit of JEVTANA is of the same order as that of abiraterone.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Prostate cancer is a life-threatening disease.
This proprietary medicinal product is intended as curative therapy.
The efficacy/adverse effects ratio is high.

Public health benefit:

The burden represented by prostate cancer is substantial: it is the most common of all cancers and, in terms of mortality, it is the fourth cause of death from cancer in men. The burden that the disease represents to the population covered by the therapeutic indication for JEVTANA (hormone-resistant metastatic prostate cancer previously treated with docetaxel) is moderate.

Improvement in the treatment of cancer is a public health need which is an established priority (French 2004 Law on Public Health).

In view of the available data, the impact of JEVTANA on morbidity and mortality is low. In the absence of data, the impact of JEVTANA on the quality of life of treated patients is not quantifiable. Nevertheless, a negative impact (safety issues) on the quality of life cannot be ruled out. Moreover, JEVTANA does not contribute any additional response to the public health need compared to the strategy currently used.

Consequently, it is not expected that JEVTANA will benefit public health in this indication.

This is a second-line treatment after the failure of first-line chemotherapy;
There are few alternative medicinal products for this stage of the disease;

The actual benefit of JEVTANA remains substantial.

4.2. Improvement in actual benefit (IAB)

The Transparency Committee considers that JEVTANA provides a moderate IAB (level III) and is an alternative to ZYTIGA in the treatment of hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

[6] de Bono JS, Logothetis C, Molina A, Fizazi K, North S, et al. Abiraterone increased survival in prostate cancer. NEJM 2011; 364: 1995-2005.

4.3. Therapeutic use

Castration-resistant prostate cancer corresponds to the advanced stage of the metastatic disease. Its prognosis is poor, with a median survival of 9 to 18 months.[7] After the failure of hormonal castration, the treatment of metastatic prostate cancer calls for systemic chemotherapy.
Docetaxel, having been associated with an improvement in overall survival,[8] constitutes the first-line treatment of choice.
By way of second-line treatment, the reintroduction of docetaxel in patients who have shown a good initial response to docetaxel with a treatment-free interval of several months could be considered; it enables a biological response to be obtained in more than half the patients with a median response time of about six months,[9,10] but with no demonstrated benefit on overall survival.
For other patients, alternative treatment is represented by either cabazitaxel or abiraterone acetate. To date, no direct comparison has been made between these two medicinal products. The safety profile of abiraterone acetate enables its use to be expanded to certain patients who could not be considered for further chemotherapy, primarily due to accumulation of toxicity from taxanes. Nonetheless, for patients whose disease has progressed rapidly under hormone therapy, cabazitaxel is a treatment option.

4.4. Target population

The target population evaluated in the TC opinion of 19 October 2011 is not modified and is recalled below:

The target population of JEVTANA corresponds to patients with hormone-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen.
The population at the metastatic stage corresponds to two sub-groups:
- patients diagnosed at the metastatic stage
- patients initially diagnosed at the localised or locally advanced stage and having subsequently progressed to a metastatic stage.

In France, the incidence of prostate cancer is estimated at 71,577 new cases per year.[11]

According to a study provided to the French Parliamentary Office for the Assessment of Health Policies (OPEPS) on prostate cancer[12], the share of stages in the diagnosis is estimated at:
- 84% for localised stages;
- 3% for locally advanced stages;
- 10% for metastatic stages.

The number of patients diagnosed at the metastatic stage can therefore be estimated at 7,160 patients for 2010.

• Patients at the localised stage in diagnosis progressing towards a metastatic stage:
The percentage progression at five years is 5% at the prostate-localised stage, and it is between 22 and 32% at the capsular invasion stage (T2 in the TNM clinical staging system).[13]
Given the distribution of clinical stages T1 (27%) and T2 (58%) in the OPEPS study, the percentage progression of the localized stage to the metastatic stage can be considered to be about 20%.

[7] Alexandre I, Rixe O. Cancer de la prostate hormonorésistant. EMC (Elsevier Masson SAS, Paris), Urologie, 18-560-A-18, 2007.
[8] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004; 351: 1502-1512.
[9] Beer TM, Gaezotto M, Henner WD, Eilers KM, Wersinger EM. Multiple cycles of intermittent chemotherapy in metastatic androgen-independent prostate cancer. Br J Cancer 2004; 81: 1425-7.
[10] Eymard JC, Oudard S, Gravis G, Ferrero JM, Theodore C, Joly F, et al. Docetaxel reintroduction in patients with metastatic hormone-refractory, docetaxel-sensitive, prostate cancer: A retrospective multicenter study (TRIADE) BJU International 2010; 106: 974-8.
[11] INCA. La situation du cancer en France. November 2010 – http://www.ecancer.fr/component/docman/doc_download/6035-la-situation-du-cancer-en-france-en-2010
[12] M. Bernard Debré, Député. Rapport sur le dépistage et le traitement du cancer de la prostate. Conclusion et Etude réalisée pour l'OPEPS en 2008 (cohorte FRANCIM-InVS 2001) 2009: 154-172.
[13] Avancès C. Cancer de la prostate: la maladie localisée. Médecine Nucléaire. 2008; 32: 46–50.

The number of prostate cancer patients diagnosed at the localized stage and progressing towards a metastatic stage is estimated to be 12,030.

• Patients at the locally advanced stage in diagnosis progressing towards a metastatic stage:
Locally advanced tumours have a rate of progression towards a metastatic stage on the order of 40% at five years.[14] The number of prostate cancer patients diagnosed at the locally advanced stage and progressing towards the metastatic stage is estimated at 860.
Altogether, the number of patients at the metastatic stage is estimated at 20,050 per year.

Ninety-six per cent (96%) of patients with metastatic cancer, i.e. 19,250 patients, are treated with hormone therapy. Of these, 48% (9,240 patients) become hormone-resistant.
Of the hormone-resistant patients, 60% are likely to receive chemotherapy. Ninety-seven percent (97%) of these patients are treated with docetaxel as first-line chemotherapy, i.e. 5,380 patients.
Of the patients still alive at the end of a first line of docetaxel-containing chemotherapy, about half[15] could be candidates for a second-line treatment, i.e. 2,690 patients.

The target population for JEVTANA is estimated at around 2,700 patients per year.

14 Soulié M et al. Place de la chirurgie dans les tumeurs de la prostate à haut risque. Cancer/Radiothérapie. 2010; 14: 493–499.
15 Unpublished observational study carried out by the company in 2010