HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 October 2011

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.

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

Reason for the request: Inclusion in the list of products for hospital use.

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
The WHO has yet to assign JEVTANA a bottom-level ATC code.

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines:

None

2.3. Medicines with a similar therapeutic aim

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

3 ANALYSIS OF AVAILABLE DATA

The efficacy and safety data for JEVTANA in the metastatic prostate cancer indication are taken from a phase III study whose results are presented below. The data from the phase I studies (studies TED6188, TED6190, TED6189) as well as those from study ARD6191 carried out in breast cancer and therefore outside the scope of the indication adopted for the MA were not taken into account.

3.1. Efficacy

TROPIC STUDY (EFC6193)[1]
A randomized, open-label, phase III study compared cabazitaxel (JEVTANA) with mitoxantrone, both combined with prednisone or prednisolone, in patients with hormone-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen.

Patients were assigned by 1:1 randomisation to treatment with either
- mitoxantrone at the dose of 12 mg/m^2 IV every three weeks and prednisone or prednisolone at the dose of 10 mg per day orally, in accordance with their MA.
- or cabazitaxel at the dose of 25 mg/m^2 IV every three weeks and prednisone or prednisolone at the dose of 10 mg per day orally.

The cycles lasted 3 weeks in both treatment groups.
Each patient was treated for up to a maximum of 10 cycles (30 weeks) or until disease progression or onset of death or the occurrence of an adverse effect judged unacceptable by the investigator.

The inclusion criteria are summarised as follows:
Patients aged ≥ 18 years, suffering from histologically or cytologically-confirmed hormone-resistant prostate adenocarcinoma previously treated with docetaxel-containing chemotherapy. Patients needed to exhibit disease progression in the 6 months following hormone therapy and during or after administration of docetaxel-containing chemotherapy.

The primary efficacy endpoint was overall survival defined as the time between randomisation and patients' death irrespective of the cause.

Secondary endpoints were:

- progression-free survival, defined as the time between randomisation and the onset of one of the following events: tumour progression assessed according to the Response Evaluation Criteria In Solid Tumours (RECIST), progression in levels of prostate-specific antigen (PSA), progression of pain, or death from any cause.
- the objective response rate (complete responses and partial responses)[2]

[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
[2] RECIST criteria: evaluation of tumour response in solid tumours: complete response (disappearance of target lesions), partial response (30% decrease in the target lesions in their largest diameter), disease progression (20% increase in the target lesions in their largest diameter) and stabilisation.

- progression in PSA levels, defined as follows:
  - in non-responder patients, as an increase greater than or equal to 25% with respect to the nadir (provided that the increase in the absolute PSA level was at least 5 ng/ml), confirmed by a second determination at least one week later.
  - in responder patients and in patients whose PSA level could not be assessed on inclusion progression was defined as an increase greater than or equal to 50% with respect to the nadir (provided that the increase in the absolute PSA level was at least 5 ng/ml), confirmed by a second determination at least one week later.
- the percentage of biological response (PSA levels), defined as a decrease greater than or equal to 50%, confirmed by a second PSA determination at least three weeks later.
- pain progression
- percentage response in terms of pain, defined as:
  - an increase greater than or equal to one point of the median PPI (present pain intensity index) with respect to the nadir, observed at two consecutive visits separated by three weeks, or
  - an increase greater than or equal to 25% of the average analgesic score with respect to the score on inclusion, observed at two consecutive visits separated by three weeks, or
  - the need to resort to palliative local radiotherapy.
- safety

Sub-group analysis:
The following prognostic factors were taken into account for the overall sub-group analysis of survival: ECOG performance status, measurable disease, number of previous lines of chemotherapy, age, country, whether pain was present or not at inclusion, PSA level, time between the last dose of docetaxel and randomisation, docetaxel dose received, and time to progression from the last dose of docetaxel.

Results:

A total of 755 patients were randomised to receive either cabazitaxel (n = 378) or mitoxantrone (n = 377). The median age of the patients was 68 years in the cabazitaxel group and 67 years in the mitoxantrone group. The majority of the patients (91.9%) had an ECOG performance status of 0 or 1.
All the patients had previously received chemotherapy (around 70% of the patients had received a single line of chemotherapy and 30% two lines of chemotherapy or more). 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 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 survival-free progression 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]).

The tumour response rate was 14.4% in the cabazitaxel group versus 4.4% in the mitoxantrone group.

The median time to progression of PSA levels was 6.4 months in the cabazitaxel group versus 3.1 months in the mitoxantrone group (HR = 0.75 95% CI: [0.63-0.90]).

The PSA response rate was 39.2% in the cabazitaxel group versus 17.8% in the mitoxantrone group, p = 0.0002.

No significant difference was observed between the two groups in terms of:

- percentage response in terms of pain:
- the median time to pain progression.

The sub-group analysis of overall survival taking prognostic factors into account showed a heterogeneous effect with, in particular, a lack of difference between cabazitaxel and mitoxantrone in patients having received three cycles or fewer (225 mg/m^2) of docetaxel.

Figure 1. Hazard ratio for overall survival as a function of the sub-groups (cabazitaxel and prednisone/prednisolone versus mitoxantrone and prednisone/prednisolone)

Factor	Sub-group	Number	HR (95% CI)
(ITT population)	All patients	755	0.70 (0.59 - 0.83)
ECOG index	0.1	694	0.68 (0.57 - 0.82)
ECOG index	2	61	0.81 (0.48 - 1.38)
Measurable disease	No	350	0.72 (0.55 - 0.93)
Measurable disease	Yes	405	0.68 (0.54 - 0.85)
No. of previous chemos	1	528	0.67 (0.55 - 0.83)
No. of previous chemos	>=2	227	0.75 (0.55 - 1.02)
Age	<65	295	0.81 (0.61 - 1.08)
Age	>= 65	460	0.62 (0.50 - 0.78)
Country	European country	402	0.68 (0.53 - 0.86)
Country	North American country	235	0.59 (0.43 - 0.82)
Country	Other countries	118	1.00 (0.65 - 1.54)
Initial pain	No	314	0.57 (0.43 - 0.77)
Initial pain	Yes	310	0.76 (0.59 - 0.98)
Initially rising PSA	No	159	0.88 (0.61 - 1.26)
Initially rising PSA	Yes	583	0.65 (0.53 - 0.80)

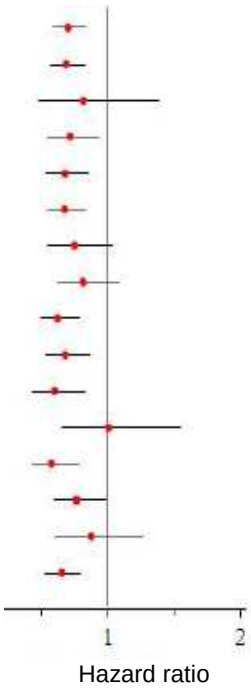
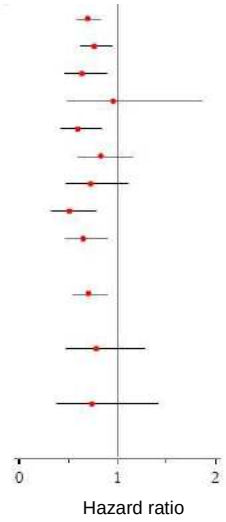


Figure 2. Hazard ratio for overall survival as a function of the dose of docetaxel and progression (cabazitaxel and prednisone/prednisolone versus mitoxantrone and prednisone/prednisolone)

Factor	Sub-group	Number	Hazard ratio (95% CI)
ITT population	All patients	755	0.70 (0.59 - 0.83)
Last dose of docetaxel until randomisation	< 6 months	504	0.77 (0.63 - 0.94)
Last dose of docetaxel until randomisation	≥ 6 months	250	0.64 (0.46 - 0.89)
Total dose of docetaxel	< 225 mg/m^2	59	0.96 (0.49-1.86)
Total dose of docetaxel	≥ 225 to 450 mg/m^2	206	0.60 (0.43 - 0.84)
Total dose of docetaxel	≥ 450 to 675 mg/m^2	217	0.83 (0.60 -1.16)
Total dose of docetaxel	≥ 675 to 900 mg/m^2	131	0.73 (0.48 -1.10)
Total dose of docetaxel	≥ 900 mg/m^2	134	0.51 (0.33 - 0.79)
Progression	During the last docetaxel treatment	219	0.65 (0.47 - 0.90)
Progression	During the first 3 months after the last dose of docetaxel	339	0.70 (0.55 - 0.91)
Progression	Between 4th and 6th month after the last dose of docetaxel	108	0.79 (0.48 -1.28)
Progression	More than 6 months after the last dose of docetaxel	84	0.74 (0.39-1.40)



3.2. Adverse effects

Treatment discontinuations due to adverse events affected 18.3% of the patients in the cabazitaxel group versus 8.4% in the mitoxantrone group. The most common events leading to treatment discontinuation in the cabazitaxel group were:

- blood system (neutropenia 2.4%),
- urinary (haematuria 1.3%),
- gastrointestinal (diarrhoea 1.1%),
- general signs (fatigue 1.1%),
- renal (acute renal failure 1.1%).

Grade ≥ 3 adverse events occurred in 57.4% of the patients in the cabazitaxel group and in 39.4% of the patients in the mitoxantrone group.

The most common grade ≥ 3 events in the cabazitaxel group related to blood system (neutropenia: 21.3% cabazitaxel versus 7.0% mitoxantrone), gastrointestinal (diarrhoea and vomiting: 6.2% and 1.9% in the cabazitaxel group versus 0.3% and 0% in the mitoxantrone group) and general disorders (asthenia 4.6% cabazitaxel versus 2.4% mitoxantrone).

3.3. Conclusion

A randomized, open-label, phase III study compared cabazitaxel (JEVTANA) with mitoxantrone, both combined with prednisone or prednisolone, in 755 patients with hormone-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen.

The median age of patients was 68 years in the cabazitaxel group and 67 years in the mitoxantrone group. Over 90% of the patients had an ECOG performance status 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]).
The biological response (decrease greater than or equal to 50% of the PSA level) 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 with, in particular, a lack of difference between cabazitaxel and mitoxantrone in patients having received three cycles or fewer (225 mg/m^2) of docetaxel.
There was no difference between the two groups in response rate in terms of pain and median time to pain progression.
There are no data available on quality of life.
Safety was not as good in the cabazitaxel group as in the mitoxantrone group.
In particular, the following were more common in the cabazitaxel group: treatment withdrawals due to adverse events (18.3% versus 8.4%), 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 company launched a study (EFC11785)[3] for the indication hormone-resistant metastatic prostate cancer after treatment with a docetaxel-containing regimen. The aim of this phase III study, for which they are currently recruiting, is to demonstrate the non-inferiority in overall survival terms of a cabazitaxel dosage of 20 mg/m^2 versus 25 mg/m^2 in combination with prednisone.
In view of the high risk of onset of serious adverse events found with a cabazitaxel dosage of 25 mg/m^2 in the pivotal trial and in anticipation of the results in this non-inferiority study, the optimum cabazitaxel dosage remains to be defined.

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

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

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

Public health benefit:

The burden represented by prostate cancer is considerable: 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 of the disease as regards 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 Law on Public Health dated 2004).

In light of the data from the clinical trial, the impact of JEVTANA on morbidity and mortality is minor. The quality of life of treated patients was not assessed in this trial. Besides, the impact of JEVTANA on quality of life is not quantifiable. JEVTANA could, however, have a negative impact on the quality of life of treated patients given the tolerability problems encountered.

Moreover, JEVTANA does not contribute any additional response to a public health need compared to the strategy currently used.

Consequently, JEVTANA is not expected to benefit public health in this indication.

This is a second-line treatment after the failure of a first-line chemotherapy;
There are few drug alternatives at this stage of the disease;

The actual benefit of JEVTANA is substantial.

4.2. Improvement in actual benefit (IAB)

JEVTANA offers a minor improvement in actual benefit (IAB IV) in the management of hormone-resistant metastatic prostate cancer previously treated with a docetaxel-containing chemotherapy regimen.

4.3. Therapeutic use

Hormone-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.[4] 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,[5] 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 better biological response to be obtained in more than half the patients with a median response time of about six months.[6, 7]

[4] Alexandre I, Rixe O. Cancer de la prostate hormonorésistant. EMC (Elsevier masson SAS, Paris), Urologie, 18-560-A-18, 2007.

[5] 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.

[6] 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.

JEVTANA constitutes a new therapeutic approach for the management of hormone-resistant metastatic prostate cancer previously treated with a docetaxel-containing chemotherapy regimen.

4.4. Target population

The target population for JEVTANA is 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.[8]

According to a study provided to the French Parliamentary Office for the Assessment of Health Policies (*OPEPS*) on prostate cancer,[9] 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).[10] Given the distribution of clinical stages T1 (27%) and T2 (58%) in the *OPEPS* study, the percentage progression of the localised stage to the metastatic stage can be considered to be about 20%.
The number of prostate cancer patients diagnosed at the localised 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 of the order of 40% at five years.[11] 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 a metastatic cancer, i.e. 19,250 patients, are treated by hormone therapy. Of these, 48% (9,240 patients) become hormone-resistant.
Of the hormone-resistant patients, 60% are likely to receive chemotherapy. Ninety-seven per cent (97%) of these patients are treated with docetaxel as a 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[12] 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.

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[7] 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.
[8] 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
[9] 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.
[10] Avancès C. Cancer de la prostate: la maladie localisée. Médecine Nucléaire. 2008; 32: 46–50.
[11] Soulié M et al. Place de la chirurgie dans les tumeurs de la prostate à haut risque. Cancer/Radiothérapie. 2010; 14: 493–499.
[12] Unpublished observational study carried out by the company in 2010

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services for the indication and at the dosage specified in the Marketing Authorisation.