



HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

29 February 2012

ZYTIGA 250 mg, tablet
B/120 tablets (CIP code: 2174974)

Applicant: JANSSEN-CILAG

Abiraterone acetate
ATC code: abiraterone (Other hormone antagonists)

Annual initial hospital prescription, restricted to oncology specialists or doctors with cancer training. Non-restricted renewal.

Date of Marketing Authorisation (centralised European procedure): 5 September 2011

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Abiraterone acetate

1.2. Indication

“ZYTIGA is indicated with prednisone or prednisolone for the treatment of metastatic castration-resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.”

1.3. Dosage

“The recommended dose is 1000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food (see information on the Method of administration). Taking the tablets with food increases systemic exposure to abiraterone (see SPC).

ZYTIGA is to be taken with low dose prednisone or prednisolone. The recommended dose of prednisone or of prednisolone is 10 mg daily.

Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly (see SPC).”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

L	Antineoplastics and immunomodulating agents
L02	Endocrine therapy
L02B	Antagonists and related agents
L01BX	Other hormone antagonists and related agents
L02BX03	Abiraterone

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

Comparator medicine not in the same therapeutic category but having a similar indication:

- JEVTANA (cabazitaxel) [AB substantial – IAB IV in treatment / TC opinion of 19 October 2011]

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

Other medicines used at this stage of the disease:

- NOVANTRONE (mitoxantrone)

“Palliative treatment (pain reduction, improved quality of life) of advanced hormone-resistant prostate cancer, in combination with low doses of corticosteroids by the oral route.”

- ESTRACYT (estramustine)

“Hormone-resistant prostate cancers.

This medicine must not be used as a first-line treatment of prostate cancer.”

3. ANALYSIS OF AVAILABLE DATA

The file submitted includes data from the phase-III pivotal study (COU-AA-301) analysed below.

3.1. Efficacy and tolerance

Study COU-AA-301^{1 2}

A randomised, double-blind phase-III study comparing the efficacy and tolerance of abiraterone (ZYTIGA) with placebo, both combined with prednisone or prednisolone, in patients affected by metastatic castration-resistant prostate cancer, previously treated with a docetaxel-based chemotherapy regimen.

The main primary efficacy endpoint was overall survival defined as the time between the randomisation date and date of death, whatever the cause.

The secondary endpoints were:

- the time to PSA progression (TTPP) defined as the time between the randomisation date and the date of PSA progression according to the PSAWG criteria. PSA progression was defined as a 25% increase in PSA after 12 weeks of treatment.
- Radiological progression-free survival defined as the time between the randomisation date and the date of radiological progression or death. Radiological progression was evaluated by the investigator and defined either by progression of the disease in the soft tissue according to the modified RECIST criteria (ganglion size ≥ 2.0 cm) or by progression of the disease observed in the imaging showing 2 new lesions or more confirmed by a second scan 6 weeks later showing 1 new additional lesion or more.
- the PSA response rate defined as the proportion of patients showing, at an interval of 12 weeks, a reduction in PSA of at least 50% compared with inclusion according to the PSAWG criteria. The PSA response rate was confirmed if an additional central laboratory measurement, carried out 4 weeks later, also showed a reduction in PSA of at least 50% compared with inclusion (again according to the PSAWG criteria).
- the objective response rate defined as the proportion of patients showing an objective response (i.e. either a complete response [CR] or a partial response [PR]) according to the RECIST criteria (tumour response based on a change in the number and size of the lesions measured by imaging).
- Modified progression free survival defined as the time between the randomisation date and the date of death or observation of one of the events: PSA progression, radiological progression, increased corticoid use, pain progression, onset of a bony event, or initiation of a new anti-cancer treatment.
- quality of life measured according to a quality of life questionnaire FACT-P (Functional Assessment of Cancer Therapy – Prostate). This is a self-questionnaire filled in by the patient that groups together items relating to patients' physical, familial, social, emotional and functional well-being (FACT-G scale) and specific items of prostate cancer (weight loss, appetite, pain, physical comfort, urinary and intestinal function). Its score ranges from 0 to 156.

¹ de Bono JS, Logothetis C, Molina A, Fizazi K, North S, et al. Abiraterone increased survival in prostate cancer. NEJM 2011;364:1995-2005.

² Antonarakis ES, Eisenberger MA. Expanding Treatment Options for Metastatic Prostate Cancer. NEJM 2011 364;21: 2055-2058.

Inclusion criteria:

- Age > 18 years
- WHO performance score: ECOG \leq 2
- Prostate adenocarcinoma confirmed histologically or cytologically without a neuro-endocrine component or small cells and that have undergone surgical or chemical castration
- At least 1 but not more than 2 previous chemotherapy lines for the metastatic disease (including at least 1 chemotherapy line with docetaxel)
- Disease progression reported by the investigator according to at least one of the following parameters:
 - PSA progression according to the PSAWG eligibility criterion (at 12 weeks, at least 25% increase in the PSA level compared with inclusion) with a PSA level > 5 ng/ml
 - radiological progression in soft tissue according to the RECIST criteria
 - progression of the bone metastases with 2 or more metastatic sites with PSA level > 5 ng/ml
- Testosterone measurement < 50 ng/dl
- Biological values within the limits indicated below:
 - Platelets \geq 100000/ μ l,
 - Serum albumin \geq 3.0 g/dl,
 - Creatinine < 1.5 x the upper limit or creatinine clearance \geq 60 ml/min,
 - Serum potassium \geq 3.5 mmol/l,
 - Bilirubin < 1.5 x ULN (upper limit of normal),
 - AST/ALT < 2.5 x ULN (upper limit of normal) or 5 x ULN in the case of liver metastases
 - Haemoglobinaemia \geq 9.0 g/dl outside of any transfusion.

The main non-inclusion criteria were: uncontrolled arterial hypertension, active or symptomatic viral hepatitis, or known chronic liver disease, elevated transaminases (ALT \geq 2.5 x normal values or bilirubin \geq 1.5 x normal values), history of renal or pituitary dysfunction, known brain metastases, prior treatment with ketoconazole.

The patients were randomised in a ratio of 2:1 into one of the two following groups:

- abiraterone group: the patients received 1000 mg of abiraterone acetate daily (four 250 mg tablets daily administered in a single dose, orally, 1 hour before or 2 hours after a meal) and 10 mg of prednisone (one 5 mg tablet twice daily, by mouth; in countries where prednisone was not available, 5 mg of prednisolone were administered twice daily), every day in 28-day “cycles”;
- placebo group: the patients received 4 tablets of placebo daily and 10 mg of prednisone (one 5 mg tablet twice daily, orally; in countries where prednisone was not available, 5 mg of prednisolone were administered twice daily), every day in 28-day “cycles”.

Patients who had not undergone an orchiectomy had to receive an LHRH agonist.

Results:

A total of 1,195 patients were randomised (ITT population): 797 patients in the abiraterone group and 398 patients in the placebo group.

The median age was 69 in each of the groups. Around two thirds of patients (70%) had already received one line of chemotherapy and 30% had received two.

Table 1: Study COU-AA-301 - Characteristics of patients at inclusion

Characteristics	abiraterone + prednisone/prednisolone N=797	placebo + prednisone/prednisolone N=398
Duration of the disease since initial diagnosis (days),		
N	791	394
Mean, days (SD)	2,610.9 (1,630.21)	2,510.1 (1,712.36)
Median, days	2,303.0	1,928.0
Range, days	175; 9,129	61; 8 996
TNM stage on initial diagnosis,		
N	797	398
II	103 (12.9%)	52 (13.1%)
III	112 (14.1%)	49 (12.3%)
IV	297 (37.3%)	160 (40.2%)
Unknown	285 (35.8%)	137 (34.4%)
Evidence of progression,		
N	797	398
Increase in PSA only	238 (29.9%)	125 (31.4%)
Radiological progression with or without an increase in PSA	559 (70.1%)	273 (68.6%)
Metastatic extension (> 10%)		
Bone	709 (89.2%)	357 (90.4%)
Ganglia	361 (45.4%)	164 (41.5%)
Lungs	103 (13.0%)	45 (11.4%)
Liver	90 (11.3%)	30 (7.6%)
Prostate mass	60 (7.5%)	23 (5.8%)
Other viscera	46 (5.8%)	21 (5.3%)
ECOG performance score,		
N	797	398
0-1	715 (89.7%)	353 (88.7%)
2	82 (10.3%)	45 (11.3%)
Pain,		
N	797	398
Present (score BIP-SF 0-3)	357 (44.8%)	179 (45.0%)
Absent (score BIP-SF 4-10)	440 (55.2%)	219 (55.0%)
Prior treatments		
N	797	398
Surgery	429 (53.8%)	193 (48.5%)
Radiotherapy	570 (71.5%)	285 (71.6%)
Hormone therapy	796 (99.9%)	396 (99.5%)
Other (including chemotherapy)	797 (100%)	398 (100%)
Time since last dose of chemotherapy,		
N	791	394
Mean, months (SD)	6.25 (7,380)	5.72 (6,084)
Median, months	3.94	3.94
Range, months	0.6; 65.9	0.4; 76.0

In an intermediate analysis laid down in the protocol, carried out following 552 deaths (333 of the patients of the abiraterone group and 219 in the placebo group), the median overall survival (primary efficacy endpoint) was 14.8 months (95% CI: [14.1; 15.4]) in the abiraterone group versus 10.9 months (95% CI: [10.2; 12.0]) in the placebo group, i.e. a difference in absolute value of 3.9 months in favour of the abiraterone group.

The median monitoring time on this analysis date was 12.8 months.

The firm's file mentions an overall survival analysis carried out 7 months later, a so-called "final analysis" when patients whose treatments in the study had failed received new treatments (35% in the abiraterone group versus 42% in the placebo group). These data did not allow reliable conclusions to be drawn and the intermediate analysis carried out following 552 deaths therefore remains the main analysis for this trial.

The median time to PSA progression was 10.2 months in the abiraterone group versus 6.6 months in the placebo group, i.e. a difference in absolute value of 3.6 months in favour of the abiraterone group.

The median radiological progression-free survival was 5.6 months in the abiraterone group versus 3.6 months in the placebo group, i.e. a difference in absolute value of 2 months in favour of the abiraterone group.

The confirmed PSA response percentage was higher in the abiraterone group than in the placebo group 29.1% versus 5.5%.

The objective response percentage (complete response or partial response according to the RECIST criteria) was 14% in the abiraterone group versus 2.8% in the placebo group. It involved mainly partial responses.

Modified progression-free survival did not differ between the abiraterone (88 days) and placebo (85 days) groups.

Only patients with a base pain score ≥ 4 were analysed, which amounts to less than half of the population included (42%) for the percentage pain palliation criterion (a reduction $\geq 30\%$ in the most intense pain felt score over the last 24 hours compared with inclusion). The proportion of patients with a reduction $\geq 30\%$ in the most intense pain felt score over the last 24 hours compared with inclusion was 44% in the abiraterone group versus 27% in the placebo group.

Analysis of the time to pain progression criteria and time to first bone event involved less than a quarter of the patients in the study. Given the reduced numbers for these criteria, the results suggested by these two analyses do not allow reliable conclusions to be drawn.

At inclusion, the quality of life scores of the FACT-P questionnaire (score ranging from 0 to 156) were similar between the two groups (score = 107 in the abiraterone group and 108 in the placebo group). At the end of the treatment, these scores were of 102.5 in the abiraterone group vs 94 in the placebo group. These reductions in the score are evidence of a deterioration in quality of life in each of the groups; however, the patients' quality of life deteriorates less when under treatment than with placebo.

3.2. Adverse effects

The frequency of grade 3 and 4 adverse events was 55% in the abiraterone group and 58% in the placebo group.

The most specific adverse events of the abiraterone treatment were peripheral oedema (all grades taken together: 31% in the abiraterone group versus 22% in the placebo group), hypokalaemia (17% versus 8% in the placebo group), urinary tract infection (12% in the abiraterone group versus 7% in the placebo group) and arterial hypertension (10% versus 8% in the placebo group).

According to the EPAR, the mineralocorticoid reactions (oedema, hypokalaemia, arterial hypertension) caused by this medicine are linked with its mechanism of action; however, the occurrence of urinary infections remains unexplained.

3.3. Conclusion

A randomised, double-blind phase-III study compared the efficacy and tolerance of abiraterone (ZYTIGA) with placebo, both combined with prednisone or prednisolone, in patients with metastatic, castration-resistant, prostate cancer previously treated with a docetaxel-based chemotherapy regimen.

An intermediate analysis laid down in the protocol, carried out following 552 deaths (333 of the patients of the abiraterone group and 219 in the placebo group), showed higher median overall survival (primary efficacy endpoint) in the abiraterone group than in the placebo group (14.8 months (95% CI: [14.1; 15.4]) in the abiraterone group versus 10.9 months (95% CI: [10.2; 12.0]) in the placebo group, i.e. a difference in absolute value of 3.9 months in favour of the abiraterone group.

The median time to a 25% PSA rate increase after 12 weeks of treatment was longer in the abiraterone group than in the placebo group (10.2 months versus 6.6 months), i.e. a difference in absolute value of 3.6 months in favour of the abiraterone group.

The median survival without radiological progression or death was longer in the abiraterone group than in the placebo group (5.6 months versus 3.6 months), i.e. a difference in absolute value of 2 months in favour of the abiraterone group.

The percentage of patients, at an interval of 12 weeks, with a PSA reduction of at least 50% compared with inclusion was higher in the abiraterone group than in the placebo group: 29.1% versus 5.5%.

The objective response percentage (complete or partial response according to the RECIST criteria) was higher in the abiraterone group than in the placebo group (14% versus 2,8%). It involved mainly partial responses.

Modified progression-free survival did not differ between the abiraterone and the placebo groups (88 days versus 85 days).

The quality of life scores of the FACT-P questionnaire (score ranging from 0 to 156) showed deterioration in each of the groups compared. However, the patients' quality of life deteriorated less under the treatment than with placebo.

The most specific adverse events of the treatment with abiraterone were peripheral oedema (all grades taken together: 31% in the abiraterone group versus 22% in the placebo group), hypokalaemia (17% versus 8% in the placebo group), urinary tract infection (12% in the abiraterone group versus 7% in the placebo group) and arterial hypertension (10% versus 8% in the placebo group).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Prostate cancer is a disease which threatens life;

This medicinal product falls into the category of a curative treatment;

The efficacy/tolerance ratio is high;

This is a second-line treatment after failure of docetaxel in patients whose tumour is castration-resistant;

There are treatment alternatives;

Public health benefit:

The burden represented by prostate cancer is substantial: it is the most frequent of all the cancers and, in terms of mortality, it is the third cause of death from cancer in men. The burden of the disease corresponding to the population coming within the therapeutic indication of ZYTIGA (metastatic castration-resistant prostate cancer in adult men whose disease has progressed during or after a docetaxel-based chemotherapy regimen) is moderate.

Improvement of cancer treatment is a public health need consistent with established priorities (Public Health Law, 2004).

In the light of the clinical trial data, ZYTIGA's effect on morbidity and mortality is moderate. The patients' quality of life deteriorates less under treatment than with placebo.

Therefore, the medicinal product ZYTIGA could provide an additional response to the public health need compared with the strategy currently used.

The method of administration could have a positive impact on organisation of care.

Consequently, a public health benefit is expected for ZYTIGA in this indication. This benefit is low.

The actual benefit of ZYTIGA is substantial.

4.2. Improvement in actual benefit (IAB)

ZYTIGA provides a moderate improvement in actual benefit (level III) in terms of efficacy and tolerance in the treatment of metastatic castration-resistant prostate cancer which progresses during or after docetaxel therapy.

4.3. Therapeutic use³

Metastatic castration-resistant prostate cancer is an advanced stage of the metastatic disease. Its prognosis is poor, with a median survival of 9 to 18 months.⁴ When hormonal castration has failed, treatment of metastatic prostate cancer turns to systemic chemotherapy. Docetaxel, which has been associated with an improvement in overall survival⁵, is the first-line treatment of choice. As second-line treatment, resumption of docetaxel in patients who had a good initial response to docetaxel with a free interval of several months can be considered; it achieves a biological response in over half of the patients for a median response time of approximately six months.^{6,7} In the other patients, the therapeutic alternative is represented by cabazitaxel which has demonstrated its superiority over mitoxantrone in terms of overall survival.

³ ALD Guide "Prostate cancer »: www.has-sante.fr. September 2008

⁴ Alexandre I, Rixe O. Hormone-resistant prostate cancer. EMC (Elsevier Masson SAS, Paris), Urology, 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.

ZYTIGA is an alternative to cabazitaxel but with a better tolerance profile, although no direct comparison has been carried out between these two medicines.

4.4. Target population

The ZYTIGA target population are patients with metastatic, castration-resistant, prostate cancer, previously treated with a docetaxel-based therapy.

The population at the metastatic stage fall into two sub-groups:

- patients diagnosed in the metastatic stage
- patients initially diagnosed in the localised or locally advanced stage who have 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 for the Parliamentary Office for Evaluation of Health Policies [OPEPS] on prostate cancer⁹, the share of the stages at diagnosis is estimated at:

- 84% for the localised stages;
- 3% for the locally advanced stages;
- 10% for the metastatic stages.

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

- Patients in the localised stage at diagnosis progressing to a metastatic stage:

The percentage progression at five years is 5% in the prostate localised stage and is between 22% and 32% when the capsule is affected (clinical stage T2 of the TNM classification).¹⁰

According to the distribution of clinical stages T1 (27%) and T2 (58%) in the OPEPS study, the percentage of progression from the localised stage to the metastatic stage can be approximated at 20%.

The number of patients with prostate cancer diagnosed in the localised stage and progressing to a metastatic stage is estimated at 12,030 patients.

- Patients in the locally advanced stage at diagnosis progressing to a metastatic stage:

Locally advanced tumours have a progression rate to a metastatic stage of around 40% at five years.¹¹ The number of patients with prostate cancer diagnosed at locally advanced stage and progressing to the metastatic stage is estimated at 860 patients.

All in all, the number of patients at the metastatic stage is estimated at 20,050 patients per year.

96% of patients with metastatic cancer are treated with hormone therapy, i.e. 19,250 patients. Of these, 48% become castration-resistant, i.e. 9,240 patients.

60% of the castration-resistant patients can receive chemotherapy. 97% of these patients are treated with docetaxel as first-line chemotherapy, i.e. 5,380 patients.

Approximately 75% of these patients (experts' opinion) would qualify for second-line treatment with ZYTIGA, i.e. 4,000 patients.

The target population of ZYTIGA is estimated at approximately 4,000 patients per year.

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. The cancer situation in 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. Report on the detection and treatment of prostate cancer. Conclusion and Study carried out for the OPEPS in 2008 (cohort FRANCIM-InVS 2001). 2009: 154-172.

¹⁰ Avancès C. Prostate cancer: the localised disease. Médecine Nucléaire. 2008; 32: 46–50.

¹¹ Soulié M et al. Place of surgery in high-risk prostate tumours. Cancer/Radiotherapy. 2010; 14: 493–499.

4.5. Transparency Committee recommendations

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

4.5.1 Packaging: Appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 100%