BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

**XTANDI** (enzalutamide), androgen receptor signalling pathway inhibitor

**Minor improvement in asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer, without indication for chemotherapy**

**Main points**

- XTANDI now has Marketing Authorisation in the treatment of metastatic castration-resistant prostate cancer in asymptomatic or mildly symptomatic patients (most intense pain score experienced during the previous 24 hours ≤ 3 on a scale from 0 to 10), after failure of androgen deprivation therapy and in whom chemotherapy is not yet clinically indicated.
- It improves radiological progression-free survival, overall survival and median time to initiation of cytotoxic chemotherapy.
- XTANDI offers a minor improvement, the same as that of ZYTIGA in the treatment of metastatic castration-resistant prostate cancer prior to treatment with docetaxel.

**Pre-existing indication**

- XTANDI already has Marketing Authorisation in metastatic castration-resistant prostate cancer during or after docetaxel-based chemotherapy.
- This summary does not cover this indication.

**Therapeutic use**

- After failure of androgen deprivation therapy (patients considered castration-resistant), in the first-line:
  - in symptomatic patients, the treatment of choice is docetaxel, which improves overall survival:
  - in asymptomatic or mildly symptomatic patients and when chemotherapy is not yet clinically indicated, ZYTIGA (abiraterone acetate) is a first-line treatment for metastatic prostate cancer. XTANDI now has Marketing Authorisation in this indication. Comparative data between XTANDI and ZYTIGA are not available due to their concurrent development.
- ZYTIGA and XTANDI have already validated their benefit in metastatic castration-resistant prostate cancer when the disease has progressed during or after docetaxel-based chemotherapy. There are no data to establish the sequential use of two hormonal therapies, XTANDI and ZYTIGA, before or after docetaxel treatment.

**Role of the medicinal product in the therapeutic strategy**

XTANDI is an alternative to ZYTIGA, administered in combination with prednisone or prednisolone, in first-line treatment of metastatic castration-resistant prostate cancer, in asymptomatic or mildly symptomatic patients after failure of androgen deprivation therapy and in whom chemotherapy is not yet clinically indicated.

**Clinical data**

- A randomised, double-blind study compared the efficacy and safety of 160 mg/day of enzalutamide with placebo in patients with metastatic castration-resistant prostate cancer, asymptomatic or mildly symptomatic, not previously treated with chemotherapy. Patients must be mildly symptomatic, i.e., have a most intense pain score experienced during the previous 24 hours ≤ 3 on a scale from 0 to 10.
- The 1,717 randomised patients (872 patients in the XTANDI group and 845 in the placebo group) had a median age of 71.5 years and 35% were 75 years of age or older. About two-thirds of the patients (67%) were symptomatic.
Two co-primary endpoints were defined: radiological progression-free survival and overall survival. Given the results obtained on these two co-primary endpoints, the study was stopped early:

- the mean radiological progression-free survival was not achieved in the XTANDI group (95% CI [13.8; not achieved] and was 3.9 months (95% CI [3.7; 5.4]) in the placebo group, HR=0.19 (95% CI [0.15; 0.23]; p<0.0001;
- in the intermediary analysis specified in the protocol, the median overall survival was not achieved in the XTANDI group (241 deaths/ 872 patients) or in the placebo group (299 deaths/ 845 patients). Overall survival medians were estimated at 32.4 months (95% CI [30.1 - not achieved] in the XTANDI group versus 30.2 months (95% CI [28.0 - not achieved] in the placebo group, i.e., an absolute gain of about 2.2 months favouring XTANDI (HR=0.71; 95% CI [0.60; 0.84]; p<0.0001). These estimated values are to be considered with caution given the small numbers involved on the dates of the estimations (4 patients in the XTANDI group and 24 patients in the placebo group) and the short follow-up period. Therefore, an update of the data is expected.

Improvements favouring XTANDI have been shown in the secondary endpoints (except for progression of pain, according to the BPI questionnaire at 6 months) and especially in the median time to initiation of cytotoxic chemotherapy, which was extended by 17.2 months with XTANDI compared with placebo: 28 months versus 10.8 months (HR=0.35; 95% CI [0.30; 0.40]; p<0.0001).

The frequency of discontinuations of treatment on account of adverse events was similar in the two groups. Grade ≥ 3 adverse events were reported in 42.9% of patients in the XTANDI group and 37.1% of patients in the placebo group.

The most common adverse events with XTANDI were asthenia, hot flushes, headaches and high blood pressure.

Overall, the safety profile in the chemotherapy-naïve population was similar to that observed in patients previously treated with docetaxel.

### Special prescribing conditions

- Initial annual hospital prescription
- Prescription restricted to cancer treatment or clinical oncology specialists and departments.

### Benefit of the medicinal product

- The actual benefit* of XTANDI in the extension of the Marketing Authorisation indication is substantial.
- Like ZYTIGA in combination with prednisone or prednisolone, XTANDI provides minor clinical added value** (CAV IV) in terms of efficacy and safety in the treatment of asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer, after failure of androgen deprivation therapy and in whom chemotherapy is not yet clinically indicated.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

---

1. **The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

2. **The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no improvement”.

© Haute Autorité de Santé 2015