HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication and investigation
June 2016

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

CASODEX (bicalutamide), antiandrogen

Substantial clinical benefit in metastatic prostate cancer, in combination with medical or surgical castration
Insufficient clinical benefit in the treatment of locally advanced prostate cancer, at high risk of disease progression, in treatment alone or as an adjuvant to radical prostatectomy or radiation therapy.

Main points

- CASODEX has Marketing Authorisation in the treatment of prostate cancer:
  - metastatic, in combination with medical or surgical castration, at a dosage of 50 mg/day
  - locally advanced prostate cancer, at high risk of disease progression, at a dosage of 150 mg/day, in treatment alone or as an adjuvant to radical prostatectomy or radiation therapy.
- Its therapeutic benefit remains substantial in metastatic prostate cancer, in combination with medical or surgical castration, at the dosage of 50 mg/day.
- With regard to current therapeutic methods, CASODEX has no role in the therapeutic strategy for locally advanced prostate cancer, at high risk of progression, at the dosage of 150 mg/day, either in treatment alone or as an adjuvant to radical prostatectomy or radiation therapy.

Therapeutic use

- The standard first-line treatment at the metastatic stage relies on surgical castration or chemical castration with hormone therapy (androgenic suppression by GnRH agonist or antagonist).
  Hormone therapy is the standard treatment as set out below:
  - early initiation
  - combination of GnRH analogue and antiandrogen during the first month, In case of treatment by a GnRH analogue, transient hypertestosteronemia (flare-up effect) may be observed. In this situation, a non-steroidal antiandrogen (flutamide, nilutamide, bicalutamide) or steroidal antiandrogen (cyproterone acetate) may be combined for a short period in order to prevent blood testosterone peaks.
  - then recommended monotherapy with GnRH analogue or surgical castration.

  During the onset of resistance to the castration, antiandrogens may also play a role in the context of complete androgen blockade, combining an antiandrogen and a GnRH agonist/antagonist, which sometimes allow to controlthe disease for several months. The long-term benefit of complete androgen blockade is unproven.
- Validated standard treatments, at the locally advanced stage, at high risk of progression, are:
  - external radiation therapy with long-term hormone therapy (2 or 3 years) by GnRH agonist or antagonist.
  - total prostatectomy with lymph node dissection (possible for some cT3a N0M0).

- **Role of the medicinal product in the therapeutic strategy**
- In the treatment of metastatic prostate cancer, CASODEX, at the dosage of 50 mg/day, remains a first-line medicine, co-prescribed with surgical or chemical castration.
- In the treatment of locally advanced prostate cancer, at high risk of disease progression, CASODEX has no role, either in treatment alone or as an adjuvant to radical prostatectomy or radiation therapy, including for the treatment of relapse, given:
  - the available efficacy data versus placebo, of low level of evidence and clinical relevance,
  - uncertainties in terms of safety, at the high dosage of 150 mg/day, for 5 years,
  - the absence of comparative data versus GnRH analogues,
  - available standard treatments according to the current clinical guidelines AFU 2013, ESMO 2015 and NCCN 2016.

Clinical data

- At the metastatic stage, at the dosage of 50 mg/day, no new efficacy data are available since the previous assessment.
- The supporting data for the CASODEX indications validated by the Marketing Authorisation in the treatment of locally advanced prostate cancer, at high risk of disease progression, either in treatment alone or as an adjuvant to radical prostatectomy or radiation therapy, at the dosage of 150 mg/day, rely on exploratory analyses of subgroups of the EPC programme. This program included 3 placebo-controlled studies in a heterogeneous population (prostate cancer at localised stage in two-thirds of cases - indication not validated by the Marketing Authorisation and locally advanced in one-third of cases). The new available data rely on an update with a median 9.7 years of follow-up for exploratory analyses in subgroups of studies from this programme:
  - in adjuvant treatment with radiation therapy: the results are comparable to those of the previous analysis, with a difference suggested in terms of progression-free survival and overall survival between the bicalutamide and placebo arms. Comparison data to analogues used for more than one decade, notably ZOLADEX (goserelin) are not available;
  - in adjuvant treatment with radical prostatectomy: the difference in progression-free survival observed in the previous analyses at 5.4 and 7.4 years was not found with the updated data at 9.7 years and no overall survival benefit was demonstrated versus placebo;
  - abstention-monitoring: as in the previous analysis at 7.4 years, a difference was observed between bicalutamide 150 mg/day and placebo in terms of progression-free survival with a percentage of events of 73.2% versus 79.1% (HR = 0.67 95% CI [0.56-0.80]) without demonstrating gain in overall survival.

  The most frequent adverse effects (> 10%) on bicalutamide remain breast sensitivity and gynecomastia.
- Overall, with regard to current therapeutic methods, the contribution of CASODEX at the dosage of 150 mg/day, either as an adjuvant to radiation therapy or prostatectomy or in treatment alone has not been demonstrated, due to:
  - the low level of evidence, based on post-hoc exploratory analyses, in subgroups, with poorly-defined risk factors as well as the absence of gain in overall survival in the total population,
  - low gain in progression-free survival (primary endpoint) versus placebo,
  - the lack of comparative data versus standard treatments used in the therapeutic strategy such as the GnRH analogue ZOLADEX (goserelin), which has had Marketing Authorisation since 1999 in adjuvant treatment with external radiation therapy in locally-advanced prostate cancer,
  - the safety profile, in particular at high dosage of 150 mg per day recommended for 5 years, with, in particular, a suspected cardiac toxicity,
  - therapeutic methods for managing prostate cancer with standard treatments validated at this stage: external radiation therapy combined with a GnRH agonist or antagonist and total prostatectomy.

Benefit of the medicinal product

- The actual clinical benefit* of CASODEX remains substantial in metastasized prostate cancer, in combination with medical or surgical castration, at the dosage of 50 mg/day.
- Recommends the continuation of inclusion on the list of reimbursable products for supply by pharmacists and for hospital use ONLY in the treatment of metastasized prostate cancer, in combination with medical or surgical castration.
- The actual clinical benefit* of CASODEX is insufficient to be reimbursed by National Health Insurance, in locally advanced prostate cancer, at high risk of disease progression, either in treatment alone or as an adjuvant to radical prostatectomy or radiation therapy, at the dosage of 150 mg/day.

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This document was created on the basis of the Transparency Committee Opinion of 08 June 2016 (CT-9627_14845) available at **www.has-sante.fr**

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