HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
23 SEPTEMBER 2020
The legally binding text is the original French opinion version

darolutamide
NUBEQA 300 mg film-coated tablets

First assessment

Key points

Favourable opinion for reimbursement in combination with androgen deprivation therapy (ADT) in the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease, defined by a prostate-specific antigen doubling time (PSA-DT) of ≤ 10 months.

What therapeutic improvement?

Therapeutic improvement in the care pathway.

Role in the care pathway?

The management of localised prostate cancer depends on the risk of progression defined using the D'Amico classification system:
- low-risk localised tumour: active surveillance or immediate treatment by prostatectomy, external radiotherapy or brachytherapy;
- intermediate-risk localised tumour: local treatment with prostatectomy or radiotherapy (+/- short-term hormone therapy);
- high risk: total prostatectomy or radiotherapy combined with prolonged hormone therapy (2-3 years).

Following local treatment (prostatectomy or radiotherapy), monitoring is put in place with, in particular, regular rectal examination and measurement of PSA levels in order to verify the absence of recurrence and assess tolerance to treatment. In the event of local recurrences, the main salvage therapies proposed are as follows:
- in the event of recurrence following prostatectomy: salvage radiotherapy, combined or not with hormone therapy;
- in the event of recurrence following radiotherapy: salvage prostatectomy and/or hormone therapy.
In the event of a further recurrence following salvage therapy and after confirming the absence of metastases following an imaging exam, continuous androgen deprivation therapy (ADT) is initiated in order to maintain serum testosterone < 50 ng/dL.

The Oncology Committee of the French Urology Association (CCAFU) defines castration-resistant prostate cancer (CRPC) as serum testosterone < 50 ng/dL along with biochemical progression (three consecutive rises in PSA, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL) or radiographic progression (≥ 2 new lesions on bone scan or progression of a measurable lesion according to RECIST criteria) despite medical or surgical castration.

In its opinions of 12 June 2019, the Transparency Committee had considered that XTANDI (enzalutamide) or ERLEADA (apalutamide), in combination with ADT, are first-line treatments in adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease, defined by a prostate-specific antigen doubling time (PSA-DT) of ≤ 10 months. No data enable positioning of the two antiandrogens, XTANDI (enzalutamide) and ERLEADA (apalutamide), relative to one another in this indication in the absence of direct comparative data due to their concomitant development. For ERLEADA (apalutamide), the Committee reiterated that patients with severe cardiovascular disease (severe or unstable angina pectoris, myocardial infarction, symptomatic congestive heart failure, venous or arterial thromboembolic events, ventricular arrhythmias) and patients with a history of seizures or disease exposing them to a risk of seizures (recent stroke, cerebral arteriovenous malformation, schwannoma, meningioma or other CNS or meningeal disorder) were not included in the protocol of the SPARTAN study and that, consequently, no clinical data are available in these populations (see section 4.4. Special warnings and precautions for use of the SPC). Similarly, the Committee highlighted the fact that the safety data from the SPARTAN study were reported following a median follow-up of 20.3 months and an apalutamide exposure duration of 16.9 months. No long-term safety data are available.

Role of the medicinal product in the care pathway

Considering the results of the ARAMIS study, with, in particular, demonstration of the superiority in terms of overall survival compared to androgen deprivation therapy alone, NUBEQA (darolutamide) is a first-line treatment in prostate cancer, following castration resistance and in the absence of metastases, in high-risk patients, defined by a prostate-specific antigen doubling time (PSA-DT) of ≤ 10 months. Androgen deprivation therapy must be maintained throughout treatment.

It is not possible to position NUBEQA (darolutamide) compared to the other two antiandrogens, XTANDI (enzalutamide) or ERLEADA (apalutamide), in this indication in the absence of direct comparative data due to their concomitant development. However, the Committee considers that the choice between these three androgen receptor inhibitors should take into account the level of evidence of each drug, its safety profile and interactions with other medicinal products and patients' preferences.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Prostate cancer is a life-threatening disease.
◗ It is a specific curative treatment for prostate cancer.
◗ The efficacy/adverse effects ratio is high.
◗ At the time the ARAMIS pivotal study was conducted, there were no clinically relevant comparators. Today, the clinically relevant comparator is XTANDI (enzalutamide) or ERLEADA (apalutamide) (cf. section "0.5. Clinically relevant comparators").
◗ NUBEQA (darolutamide) is a first-line treatment.

◗ Public health impact (see paragraphs 04. Medical need and 07.5 Summary and discussion)
Considering:
- the seriousness of the disease,
- its incidence,
- the medical need partially met by the available alternatives,
- demonstration of an impact of NUBEQA (darolutamide) compared to placebo, both in combination with androgen deprivation therapy, in terms of metastasis-free survival, time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer and time to first symptomatic skeletal event,
- the demonstrated impact on mortality, but the absence of demonstrated impact on the care and/or life pathway of patients and the absence of demonstrative data on quality of life,

NUBEQA (darolutamide) is unlikely to have an impact on public health.

Given all these elements, the Committee deems that the clinical benefit of NUBEQA (darolutamide) in combination with ADT is substantial in the treatment of adult men with non-metastatic castration resistant prostate cancer who are at high risk of developing metastatic disease, defined by a prostate-specific antigen doubling time (PSA-DT) of ≤ 10 months.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the marketing authorisation indication and dosages.

◗ **Recommended reimbursement rate: 100%**

Clinical Added Value

Considering:

- **demonstration of the superiority of NUBEQA (darolutamide) compared to placebo, both in combination with androgen deprivation therapy (ADT), in terms of metastasis-free survival (primary endpoint) with a substantial additional effect size corresponding to an absolute increase of 22 months,**
- **demonstration of an increase in overall survival, a ranked secondary endpoint, during the final analysis, (HR = 0.685, $CI_{95\%}$ [0.533; 0.881], p=0.003),**
- **the demonstrated superiority in terms of time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer and time to first symptomatic skeletal event (other ranked secondary endpoints),**
- **the safety profile of NUBEQA (darolutamide) in combination with ADT compared to the placebo plus ADT combination with, respectively, 30.3% and 25.1% grades ≥ 3 adverse events during the double-blind period,**

the Committee deems the NUBEQA (darolutamide) in combination with ADT provides moderate clinical added value (CAV III), like XTANDI (enzalutamide) or ERLEADA (apalutamide), in the care pathway for the treatment of adult men with non-metastatic castration resistant prostate cancer who are at high risk of developing metastatic disease, defined by a prostate-specific antigen doubling time (PSA- DT) of ≤ 10 months.