Enzalutamide (Xtandi®) for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT)

General information

Drug description	Indication [1]
Enzalutamide is an androgen-receptor inhibitor.	Enzalutamide is indicated for the treatment of adult men with mHSPC in combination with ADT.

Current treatment [2]

- For men with mHSPC, NICE guidelines recommend:
  - bilateral orchidectomy or continuous LHRH agonist therapy
  - anti-androgen monotherapy with bicalutamide; or
  - combined androgen blockade (not first-line).
- NICE has also published an evidence summary for the off-label use of docetaxel (in combination with ADT) for the treatment of mHSPC. Docetaxel is licensed in the UK for the treatment of metastatic hormone-resistant prostate cancer. A draft of an update to the NICE guideline for prostate cancer recommends offering docetaxel to people who do not have significant comorbidities, starting treatment within 12 weeks of starting ADT, to be administered in six 3-weekly cycles with or without daily prednisolone.
- Although not currently recommended by NICE, abiraterone is licensed for the treatment of newly diagnosed, high-risk mHSPC in adult men in combination with ADT plus prednisone or prednisolone.

Regulatory status

EMA [1]

Approval status for this indication: On 25 March 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Xtandi®.

<u>The CHMP adopted an extension to the existing indication as follows:</u>

- Xtandi® is indicated for the treatment of adult men with mHSPC in combination with ADT.

Other indications: Xtandi® is indicated for:

- the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC).
- the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

FDA [3]

Approval status for this indication: On 16 December 2019, the FDA approved enzalutamide (Xtandi®) for patients with metastatic castration-sensitive prostate cancer (mCSPC).

Other indications: Xtandi® is indicated for

- the treatment of patients with castration-resistant prostate cancer.

Costs

112 Xtandi® tablets 40 mg = € 2,754.84 (ex-factory price) [4]

ARCHES trial patients (enzalutamide + ADT group) received enzalutamide at a dose of 160 mg daily; median treatment duration was 12.8 months [5].

According to this dosing regimen, **28 days** of enzalutamide treatment would cost **€ 2,754.84**.

Warnings and precautions [6]

- **Seizure** occurred in 0.5% of patients receiving Xtandi®. In patients with predisposing factors, seizures were reported in 2.2% of patients. Permanently discontinue Xtandi® in patients who develop a seizure during treatment.
- **Posterior reversible encephalopathy syndrome:** Discontinue Xtandi®.
- **Hypersensitivity**: Discontinue Xtandi®.
- **Ischemic Heart Disease**: Optimize management of cardiovascular risk factors. Discontinue Xtandi® for Grade 3-4 events.
- **Falls and Fractures** occurred in 11% and 10% of patients receiving Xtandi®, respectively. Evaluate patients for fracture and fall risk, and treat patients with bone-targeted agents according to established guidelines.
- **Embryo-Foetal Toxicity**: Xtandi® can cause foetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception.

Study characteristics [5, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ARCHES NCT02677896	1,150	enzalutamide (160 mg/day) plus ADT	placebo plus ADT	radiographic PFS (rPFS)	multinational, double-blind, randomized, placebo-controlled, phase III trial	-	Astellas Pharma and Pfizer	[5]

Efficacy (I vs. C)

Radiographic progression: n=79 (13.8%) vs. n=188 (32.6%)
Median rPFS, months: NR vs. 19.0, HR 0.39, 95% CI, 0.30-0.50; p<0.001
Median time to PSA progression (months): NR vs. NR, HR 0.19, 95%CI, 0.13-0.26; p<0.001
Median time to initiation of new antineoplastic therapy (months): 30.2 vs. NR, HR 0.28, 95%CI 0.20-0.40; p<0.001
Objective response rate: n=147 (83.1%) vs. n=116 (63.7%); p<0.001
Complete response: n=65 (36.7%) vs. n=42 (23.1%)
Partial response: n=82 (46.3%) vs. n=74 (40.7%)
Stable disease: n=17 (9.6%) vs. n=43 (23.6%)
Progressive disease: n=7 (4.0%) vs. n=9 (4.9%)
NE/NA: n=6 (3.4%) vs. n=14 (7.7%)
Median time to deterioration of urinary symptoms (months): NR vs. 16.8, HR 0.88, 95% CI, 0.72-1.08; p=0.2162
Median OS (months): NR vs. NR, HR 0.81, 95%CI,0.53-1.25, p=0.3361

Pre-specified sensitivity analyses of time to pain progression from the patient-reported outcome statistical analysis plan:
Median time to worst pain (item 3) (months): 14.1 vs. 11.1, HR 0.82, 95%CI, 0.69-0.98; p=0.0322
Median time to pain severity (months): 19.4 vs. 16.8, HR 0.79, 95% CI, 0.65-0.97; p=0.0209

Mean Functional Assessment of Cancer Therapy–Prostate total score was high at baseline for both treatment groups and remained high over time.
Enzalutamide plus ADT did not significantly affect **time to deterioration in urinary symptoms or QoL** compared with placebo plus ADT.

Safety (I vs. C)

Grade ≥3 AEs: n=139 (24.3%) vs. n=147 (25.6%)
Grade ≥3 SAEs: n=84 (14.7%) vs. n=90 (15.7%)
Drug-related serious AEs: n=22 (3.8%) vs. n=16 (2.8%)
AEs leading to death: n=14 (2.4%) vs. n=10 (1.7%)
AEs leading to withdrawal of treatment: n=41 (7.2%) vs. n=30 (5.2%)

Death within 24 weeks of treatment discontinuation in the absence of radiographic progression: n=12 (2.1%) vs. n=13 (2.3%)

ESMO-MCBS version 1.1 [10]

The ESMO-MCBS is not applicable since no scorable endpoint had been reached at the time of analysis.

Risk of bias (study level) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	yes	unclear[1]	yes[2]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, MG=median gain, n=number of patients, NA=not applicable, NE=not evaluable, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

[1] ARCHES trial is ongoing until May, 2021.
[2] The senior academic authors and employees of the study sponsors were responsible for the study design. Data analyses were performed by the study sponsors and provided to all authors. A professional medical writer, funded by the sponsors, assisted in the preparation of the manuscript.

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