03.01.2021

רופא/ה רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא ועלון לצרכן של

Xtandi 40mg - soft capsules

חומר פעיל:

Enzalutamide 40 mg

להלן עדכונים בעלון לרופא (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן בצהוב משמעותו החמרה):

[…]

4.1 Therapeutic indications

Xtandi is indicated for:

- the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (see section 5.1).
- the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) (see section 5.1).
- 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 (see section 5.1)
- the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

[…]

4.4 Special warnings and precautions for use

Risk of seizure
Use of enzalutamide has been associated with seizure (see section 4.8). The decision to continue treatment in patients who develop seizures should be taken case by case.

[…]

4.7 Effects on ability to drive and use machines

Xtandi may have moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizure have been reported (see section 4.8). Patients should be advised of the potential risk of experiencing a psychiatric or neurological event while driving or operating machines. No studies to evaluate the effects of enzalutamide on the ability to drive and use machines have been conducted.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions are asthenia/fatigue, hot flush, hypertension and fall. Other important adverse reactions include fractue, cognitive disorder, and neutropenia.

Seizure occurred in 0.5% of enzalutamide-treated patients, 0.1% of placebo-treated patients, and 0.3% in bicalutamide-treated patients.

תא דואר 11458 ראש העין, מספר טלפון: 03-7501166

[…]

Table 1: Adverse reactions identified in controlled clinical trials and post-marketing

MedDRA System organ class	Frequency
Blood and lymphatic system disorders	Uncommon: leucopenia, neutropenia Not known*: thrombocytopenia
Immune system disorders	Not known*: face oedema, tongue oedema, lip oedema, pharyngeal oedema
Psychiatric disorders	Common: anxiety Uncommon: visual hallucinations
Nervous system disorders	Common: headache, memory impairment, amnesia, disturbance in attention, restless legs syndrome Uncommon: cognitive disorder, seizure[¥] Not known*: posterior reversible encephalopathy syndrome
Cardiac disorders	Common: ischemic heart disease[†] Not known*: QT-prolongation (see sections 4.4 and 4.5)
Vascular disorders	Very common: hot flush, hypertension
Gastrointestinal disorders	Not known*: nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Common: dry skin, pruritus Not known*: rash
Musculoskeletal and connective tissue disorders	Common: fractures[‡] Not known*: myalgia, muscle spasms, muscular weakness, back pain
Reproductive system and breast disorder	Common: gynaecomastia
General disorders and administration site conditions	Very common: asthenia, fatigue
Injury, poisoning and procedural complications	Very common: fall

[…]

Description of selected adverse reactions

Seizure
In controlled clinical studies, 21 patients (0.5%) experienced a seizure out of 4081 patients treated with a daily dose of 160 mg enzalutamide, whereas three patients (0.1%) receiving placebo and one patient (0.3%) receiving bicalutamide, experienced a seizure. Dose appears to be an important […]

Ischemic Heart Disease
In randomized placebo-controlled clinical studies, ischemic heart disease occurred in 2.8% of patients treated with enzalutamide plus ADT compared to 1.3 % patients treated with placebo plus ADT.
[…]

5.1 Pharmacodynamic properties

[…]
Clinical efficacy and safety
Efficacy of enzalutamide was established in three randomised placebo-controlled multicentre phase 3 clinical studies [MDV3100-14 (PROSPER), CRPC2 (AFFIRM), MDV3100-03 (PREVAIL)] of patients with progressive prostate cancer who had disease progression on androgen deprivation therapy [(LHRH) analogue or after bilateral orchiectomy]. The PREVAIL study enrolled metastatic CRPC chemotherapy-naïve patients; whereas the AFFIRM study enrolled metastatic CRPC patients who had received prior docetaxel; and the PROSPER study enrolled patients with non-metastatic CRPC. Additionally, efficacy in patients with mHSPC was also established in one randomized, placebo-controlled multicentre phase 3 clinical study [NCT02677896 (ARCHES)]. All patients continued on a LHRH analogue or had bilateral orchiectomy.

In the active treatment arm, Xtandi was administered orally at a dose of 160 mg daily. In the four clinical studies (ARCHES, PROSPER, AFFIRM and PREVAIL), patients received placebo in the control arm and patients were allowed, but not required, to take prednisone (maximum daily dose allowed was 10 mg prednisone or equivalent).

Changes in PSA serum concentration independently do not always predict clinical benefit. Therefore, in the four studies it was recommended that patients be maintained on their study treatments until discontinuation criteria were met as specified below for each study.

ARCHES (NCT02677896): XTANDI versus Placebo in Metastatic CSPC

ARCHES enrolled 1150 patients with mHSPC who were randomized 1:1 to receive XTANDI orally at a dose of 160 mg once daily (N=574) or placebo orally once daily (N=576). All patients in the trial received a GnRH analog or had a prior bilateral orchiectomy. Patients were stratified by volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1-5 cycles, or 6 prior cycles). High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Treatment with concurrent docetaxel was not allowed. Patients continued treatment until radiographic disease progression, initiation of new treatment, unacceptable toxicity, or withdrawal.
The following patient demographics and baseline characteristics were balanced between the two treatment arms. The median age at randomization was 70 years (range: 42-92) and 30% were 75 years of age or older. The racial distribution was 81% Caucasian, 14% Asian, and 1% Black. Sixty-six percent (66%) of patients had a Gleason score of $\geqslant$ 8. Thirty-seven percent (37%) of patients had a low volume of disease and 63% of patients had a high volume of disease. Eighty-two percent (82%) of patients had no prior docetaxel treatment; 2% of patients had 1 to 5 cycles of docetaxel and 16% of patients had 6 prior cycles of docetaxel treatment. Twelve percent (12%) of patients received concomitant bone-targeted agents (bisphosphonates or RANKL inhibitors) which included both prostate and non-prostate cancer indications. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score was 0 for 78% of patients and 1 for 22% of patients at study entry.
The major efficacy outcome measure was radiographic progression-free survival (rPFS) based on blinded independent central review (BICR). Radiographic progression-free survival was defined as the time from randomization to radiographic disease progression at any time or death within 24 weeks after study drug discontinuation. Radiographic disease progression was defined by identification of 2 or more new bone lesions on a bone scan with confirmation (Prostate Cancer Working Group 2 criteria) and/or progression in soft tissue disease. Time to new antineoplastic therapy was an additional efficacy endpoint.
XTANDI demonstrated a statistically significant improvement in rPFS compared to placebo. Consistent rPFS results were observed in patients with high or low volume of disease and patients with and without prior docetaxel therapy. Overall survival (OS) data were not mature at the time of rPFS analysis (7.3% deaths in the ITT population had been reported). Efficacy results for rPFS from ARCHES are summarized in Table 2 and Figure 1.

Table 2. Efficacy Results in ARCHES based on BICR (Intent-to-Treat Analysis)

	XTANDI (N = 574)	Placebo (N=576)
Radiographic Progression-free Survival		
Number of events (%)	89 (15.5)	198 (34.4)
Radiographic disease progression	77 (13.4)	185 (32.1)
Death within 24 weeks after treatment discontinuation	12 (2.1)	13 (2.3)
Median, months (95% CI)[1]	NR	19.4 (16.6, NR)
Hazard ratio (95% CI)[2]	0.39 (0.30, 0.50)	
P-value[3]	p < 0.0001	

NR = Not reached
1. Based on Kaplan-Meier estimates.
2. Hazard Ratio is based on a Cox regression model stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no).
3. P-value is based on a stratified log-rank test by volume of disease (low vs high) and prior docetaxel use (yes or no).

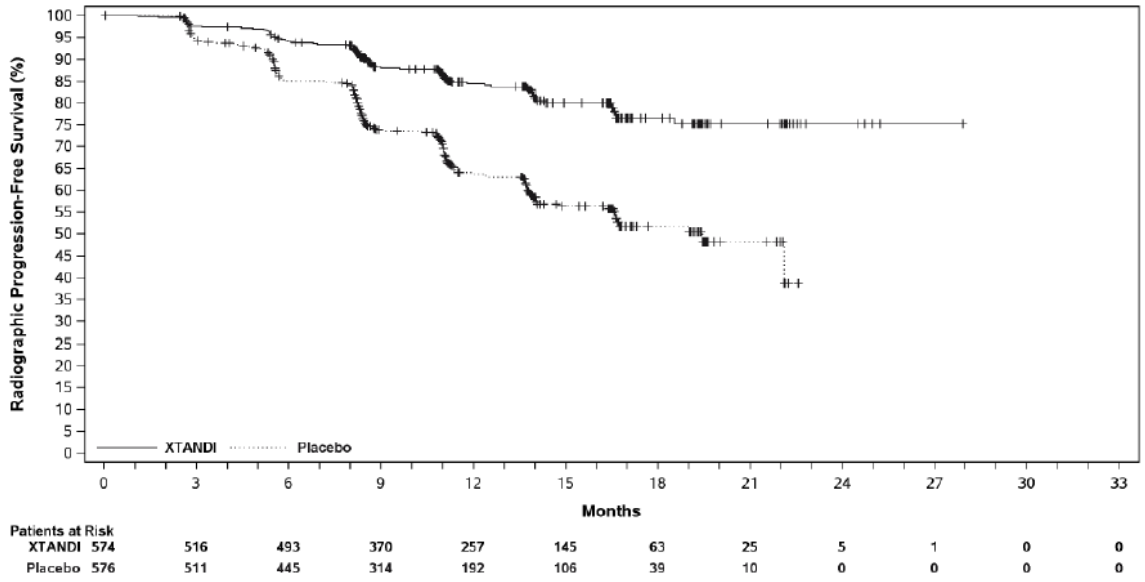

Figure 1. Kaplan-Meier Curves of rPFS in ARCHES (Intent-to-Treat Analysis)

A statistically significant improvement was also reported on the XTANDI arm compared to placebo in time to initiation of a new antineoplastic therapy (HR = 0.28 [95% CI: 0.20, 0.40]; p < 0.0001).

[…]
Additional secondary endpoints included time to first use of cytotoxic chemotherapy and chemotherapy-free survival. See results below (Table 3).
[…]
Table 3: Summary of efficacy results in the PROSPER study (intent-to-treat analysis)
[…]

Figure 2: Kaplan-Meier Curves of metastasis-free survival in the PROSPER study (intent-to-treat analysis)
[…]

Figure 3: Kaplan-Meier curves of time to first use of new antineoplastic therapy in the PROSPER study (intent-to-treat analysis)
[…]

Figure 4: Kaplan-Meier Curves of progression-free survival in the STRIVE study (intent-to-treat analysis)
[…]

An updated survival analysis was conducted when 784 deaths were observed. Results from this analysis were consistent with those from the interim analysis (Table 4, Figure 5). At the updated analysis 52% of enzalutamide-treated and 81% of placebo-treated patients had received subsequent therapies for metastatic CRPC that may prolong overall survival.
[…]

Table 4: Overall survival of patients treated with either enzalutamide or placebo in the PREVAIL study (intent-to-treat analysis)
[…]

Figure 5: Kaplan-Meier curves of overall survival based on updated survival analysis in the PREVAIL study (intent-to-treat analysis)
[…]

Figure 6: Updated overall survival analysis by subgroup: Hazard ratio and 95% confidence interval in the PREVAIL study (intent-to-treat analysis)
[…]

The median rPFS was not reached (95% CI: 13.8, not reached) in the enzalutamide-treated group and was 3.9 months (95% CI: 3.7, 5.4) in the placebo-treated group (Figure 7).
[…]

Figure 7: Kaplan-Meier curves of radiographic progression-free survival in the PREVAIL study (intent-to-treat analysis)
[…]

The protocol pre-specified interim analysis after 520 deaths showed a statistically significant superiority in overall survival in patients treated with enzalutamide compared to placebo (Table 5 and Figures 8 and 9).

Table 5: Overall survival of patients treated with either enzalutamide or placebo in the AFFIRM study (intent-to-treat analysis)

[…]

Figure 8: Kaplan-Meier curves of overall survival in the AFFIRM study (intent-to-treat analysis)

[…]

Figure 9: Overall survival by subgroup in the AFFIRM study – Hazard ratio and 95% confidence interval

[…]

Elderly
Of the 4081patients in the controlled clinical trials who received enzalutamide, 3194 patients (78%) were 65 years and over and 1426patients (35%) were 75 years and over. No overall differences in safety or effectiveness were observed between these older patients and younger patients.
[…]

5.2 Pharmacokinetic properties
[…]

Renal impairment
No formal renal impairment study for enzalutamide has been completed. Patients with serum creatinine > 177 µmol/L (2 mg/dL) were excluded from clinical studies. Based on a population pharmacokinetic analysis, no dose adjustment is necessary for patients with calculated creatinine clearance (CrCL) values ≥ 30 mL/min (estimated by the Cockcroft and Gault formula).
[…]

Race
Most patients in the controlled clinical studies (> 77%) were Caucasian. Based on pharmacokinetic data from studies in Japanese and Chinese patients with prostate cancer, there were no clinically relevant differences in exposure among the populations. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.
[…]

5.3 Preclinical safety data
[…]
Daily dosing of rats for two years with enzalutamide at 10–100 mg/kg/day produced an increased incidence of neoplastic findings (compared to control) that were considered related to the primary pharmacology of enzalutamide. These included benign thymoma, fibroadenoma in the mammary glands, and benign Leydig cell tumour in the testes in males; benign granulosa cell tumour in the ovaries in females; and adenoma in the pars distalis of the pituitary in both sexes. The most prominent of these were benign Leydig cell tumours, urothelium papilloma, and carcinoma of urinary bladder. Benign Leydig cell tumours are generally not considered relevant to humans based on experience with other anti-androgens. Some urothelium papilloma and carcinoma of urinary bladder were observed at the 100 mg/kg/day dose and are considered secondary to the irritation caused by the increased urinary crystal/calculi expected in rats based on the horizontal structure of the rat urinary bladder. Other tumours, which are also potentially related to the primary pharmacology include fibroadenoma of mammary glands and benign thymoma of thymus in males, benign granulosa cell tumours of ovaries in females, and adenoma of pituitary pars distalis in both sexes. The human relevance of thymoma, pituitary adenoma and fibroadenoma in rats is unclear, but a potential relevance cannot be ruled out. The exposure levels achieved in this study in male rats at Week 26 at 100 mg/kg per day for enzalutamide plus its active metabolites M1 and M2 (AUC_{24}: enzalutamide ~457 µg•h/mL, M1 ~321 µg•h/mL, M2 ~35 µg•h/mL) were less than or similar to those in prostate cancer patients at the recommended dose (160 mg/day) of enzalutamide (AUC_{24}: enzalutamide ~322 µg•h/mL, M1 ~193 µg•h/mL, M2 ~278 µg•h/mL).

[…]
6.6 Special precautions for disposal and other handling

Xtandi should not be handled by persons other than the patient or his caregivers. Based on its mechanism of action and embryo-fetal toxicity observed in mice, Xtandi may harm a developing fetus. Women who are or may become pregnant should not handle damaged or opened Xtandi capsules without protection, e.g., gloves. See section 5.3 Pre-clinical safety data.

[...]

להלן העדכונים בעלון לצרכן (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן בצהוב משמעותו החמרה):

[...]

1. למה מיועדת התרופה?

התרופה מיועדת לטיפול בגברים עם סרטן ערמונית אשר:
- אינו מגיב עוד לטיפול הורמונלי או לניתוח להורדת רמת טסטוסטרון
או
- התפשט לאזורים אחרים בגוף ומגיב לטיפול הורמונלי או ניתוחי להורדת רמת טסטוסטרון.

[...]

2. **לפני שימוש בתרופה**

- פרכוסים:

פרכוסים דווחו ב- 5 מקרים לכל 1,000 מטופלים שנטלו את אקסטנדי, ובפחות מ- 1 מתוך 1,000 מטופלים שקיבלו פלצבו (ראה "אם אתה לוקח, או אם לקחת לאחרונה ,תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח" בהמשך סעיף זה וסעיף 4 "תופעות לוואי").

[...]

נהיגה ושימוש במכונות: לאקסטנדי עלולה להיות השפעה בינונית על היכולת שלך לנהוג ולהשתמש במכונות. פרכוסים דווחו במטופלים הנוטלים אקסטנדי. אם אתה בסיכון מוגבר לפרכוסים דבר עם הרופא שלך.

[...]

4. תופעות לוואי.

[...]

פרכוסים: דווחו ב- 5 מטופלים מתוך 1,000 שלקחו אקסטנדי ובפחות מ-1 מתוך 1,000 מטופלים שקיבלו פלצבו. הסיכון לפרכוסים מוגבר באם אתה נוטל מינון גבוה מהמינון המומלץ, אם אתה נוטל תרופות מסוימות נוספות או באם יש לך גורמי סיכון לפרכוסים.

[...]

תסמונת אנצפלופתיה אחורית הפיכה: (יכולה להשפיע על עד 1 מתוך 1000 מטופלים)

תסמונת אנצפלופתיה אחורית הפיכה הינה מצב נדיר והפיך שמערב את המוח. דווחו מקרים נדירים של התסמונת במטופלים שטופלו באקסטנדי. אם אתה סובל מהתקף פרכוסי, החמרה בכאב הראש, בלבול, עיוורון או בעיות ראיה אחרות, יש ליצור קשר עם הרופא שלך מוקדם ככל האפשר.

[...]

תופעות לוואי נוספות:

-תופעות לוואי שכיחות מאוד (מופיעות ביותר מ-1 מתוך 10 מטופלים):

☐

[...]

☐ נפילות.

-תופעות לוואי שכיחות (מופיעות ב-עד 1 מתוך 10 מטופלים):

☐ כאבי ראש.

☐ שברים

[...]

☐ שכחה.

[...]

העלונים לרופא ולצרכן נשלחו למאגר התרופות שבאתר משרד הבריאות www.health.gov.il לצורך העלאתם לאתר וניתן לקבלם מודפסים על ידי פניה לבעל הרישום אסטלס פארמה אינטרנשונל בי.וי., ת.ד. 11458, ראש העין, מספר טלפון: 03-7501166.

בברכה

גל פרידמן

רוקח ממונה