08 נובמבר 2018

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

הנדון:
Xofigo - קסופיגו
Solution for injection
Radium-223 dichloride 1100 kBq/mL at reference date

אנו מבקשים להודיעכם שעלון האריזה במתכונת עלון לרופא של התכשיר עודכן.
העדכון כולל גם מידע הנוגע למחקר ERA-223.

ההתוויה המאושרת לתכשיר:

Treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

בפירוט שלהלן מופיע, מתוך כל פרק ששונה בעלון, רק המידע שהתעדכן. תוספת טקסט מסומנת בקו תחתון.
מחיקת טקסט מסומנת ~~בקו חוצה~~.

העדכונים בעלון האריזה במתכונת עלון לרופא

4.4 Special warnings and precautions for use

Combination with abiraterone and prednisone/prednisolone or with ~~second generation androgen receptor antagonists such as enzalutamide~~ systemic cancer therapies other than LHRH analogues

An interim analysis from a clinical trial in chemotherapy-naïve patients with asymptomatic or mildly symptomatic castration resistant prostate cancer and progressive disease with bone metastases showed an increased ~~incidence~~ risk of fractures and ~~deaths~~ a trend for increased mortality among patients receiving Xofigo in combination with abiraterone acetate and prednisone/prednisolone compared to patients receiving placebo in combination with abiraterone acetate and prednisone/prednisolone (see section 5.1).

~~Concurrent use of bisphosphonates or denosumab reduced the incidence of fractures in both treatment arms.~~
Therefore, Xofigo is contraindicated in combination with abiraterone acetate and prednisone/prednisolone (see section 4.3).

~~The s~~Safety and efficacy of Xofigo in combination with ~~second generation androgen receptor antagonists such as enzalutamide~~ cancer therapies other than LHRH analogues have not been established; an increased risk of mortality and fractures is possible. The combination of radium-223 with other systemic cancer therapies other than LHRH analogues is therefore not recommended.

Data on a safe period after which Xofigo can be administered following treatment with abiraterone acetate in combination with prednisone/prednisolone and vice versa is limited. Based on the elimination half-life of Xofigo and abiraterone, it is recommended that subsequent treatment with Xofigo is not initiated for at least 5 days after the last administration of abiraterone acetate in combination with prednisone/prednisolone. Subsequent systemic cancer treatment should not be initiated for at least 30 days after the last administration of Xofigo.

Treatment of patients with asymptomatic or mildly symptomatic bone metastases

An increased risk of death and fractures was observed in a clinical study, where Xofigo was added to abiraterone acetate and prednisone/prednisolone in patients with asymptomatic or mildly symptomatic castration resistant prostate cancer.

Treatment benefit of Xofigo in adults with castration-resistant prostate cancer and only asymptomatic bone metastases is not established. The use of Xofigo is therefore not recommended for treatment of adults with castration-resistant prostate cancer and only asymptomatic bone metastases. In adults with castration-resistant prostate cancer and mildly symptomatic bone metastases the benefit of treatment should be carefully assessed to outweigh the risks considering that high osteoblastic activity is likely to be required for treatment benefit (see section 5.1).

Patients with a low level of osteoblastic bone metastases

In clinical studies, patients with fewer than 6 bone metastases had an increased risk of fractures and did not have a statistically significant survival benefit. A pre-specified subgroup analysis also showed that overall survival was not significantly improved in patients with a total ALP < 220 U/L. Therefore in patients with a low level of osteoblastic bone metastases radium-223 is not recommended (see section 5.1).
…

Bone fractures

Xofigo increases the risk of bone fractures. In a clinical study, the addition of Xofigo to abiraterone acetate and prednisone/prednisolone, increased the incidence of fractures approximately three-fold in the Xofigo arm (see sections 4.8 and 5.1). Increased fracture risk has been found especially in patients with medical history of osteoporosis and in patients with less than 6 bone metastases. Xofigo is believed to accumulate at sites of high bone turnover such as sites of degenerative bone disease (osteoporosis) or recent (micro-)fracture increasing the risk of fractures. Other factors such as concomitant use of steroids may further increase the risk of fracture.

Prior to starting radium-223 bone status (e.g. by scintigraphy, bone mineral density measurement) and baseline risk of fractures of patients (e.g. osteoporosis, less than 6 bone metastases, medication increasing fracture risk, low body mass index) should be carefully assessed, and closely monitored for at least 24 months. Preventive measures such as the

use of bisphosphonates or denosumab should be considered before starting or resuming treatment with Xofigo (see section 4.8). In patients with a high baseline risk of fracture, the benefit of treatment should be carefully assessed to outweigh the risk. In patients with bone fractures, orthopaedic stabilisation of fractures should be performed before starting or resuming treatment with Xofigo.
…

Excipients with known effect

Depending on the volume administered, this medicinal product can contain up to 2.35 mmol (54 mg) sodium per dose, equivalent to 2.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult. ~~To be taken into consideration by patients on a controlled sodium diet.~~

4.7 Effects on ability to drive and use machines

~~There is neither evidence nor is it expected that~~ Xofigo has no or negligible influence on ~~will affect~~ the ability to drive ~~or~~ and use machines.

4.8 Undesirable effects
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The **most frequently** observed adverse reactions (≥ 10%) in patients receiving Xofigo were diarrhoea, nausea, vomiting ~~and~~ ,thrombocytopenia and bone fracture.
…

הטבלה שלהלן עודכנה עם תוספת המידע:

Table 1: Adverse reactions reported in clinical trials in patients treated with Xofigo

System Organ Class (MedDRA)	Very common	Common	Uncommon
…	…	…	…
Musculoskeletal and connective tissue disorders	Bone fracture		Osteoporosis

Description of selected adverse reactions

Bone fractures
Xofigo increases the risk of bone fractures (see section 5.1). In clinical studies, concurrent use of bisphosphonates or denosumab reduced the incidence of fractures in patients treated with radium-223 monotherapy. Fractures have occurred for up to 24 months after the first dose of radium-223.
…

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Therapeutic radiopharmaceuticals, other therapeutic radiopharmaceuticals, various therapeutic radiopharmaceuticals, ATC code: V10XX03

Clinical efficacy and safety

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Subgroup survival analysis

Subgroup survival analysis showed a consistent survival benefit for treatment with Xofigo, independent of ~~total alkaline phosphatase (ALP)~~, use of bisphosphonates at baseline and prior use of docetaxel.

A statistically significant overall survival benefit of treatment could not be demonstrated in the subgroups of patients with fewer than 6 metastases (HR for radium-223 to placebo 0.901; 95% CI [0.553 -1.466], p=0.674) or a baseline total alkaline phosphatase (ALP) < 220 U/L (HR 0.823; 95% CI [0.633 -1.068], p=0.142) in the phase III ALSYMPCA study. Therefore, efficacy may be diminished in patients with a low level of osteoblastic activity from their bone metastases.

…

Combination with abiraterone and prednisone/prednisolone

The clinical efficacy and safety of concurrent initiation of Xofigo, abiraterone acetate and prednisone/prednisolone treatment was assessed in a randomized, placebo-controlled multicenter phase III study (ERA-223 trial) in 806 chemotherapy-naïve patients with asymptomatic or mildly symptomatic castration resistant prostate cancer with bone metastases. The study was unblinded early based on an Independent Data Monitoring Committee Recommendation. At an interim analysis, an increased incidence of fractures (~~26.0%~~28.6% ~~vs 8.1%~~ 11.4%) and ~~deaths~~ reduced median overall survival (30.7 months versus 33.3 months, HR 1.195, 95% CI [0.950 - 1.505], p=0.13) ~~(34.7% vs 28.2%)~~ was observed among patients receiving Xofigo in combination with abiraterone acetate and prednisone/prednisolone compared to patients receiving placebo in combination with abiraterone acetate and prednisone/prednisolone ~~was observed~~.

עלון האריזה במתכונת עלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://www.old.health.gov.il/units/pharmacy/trufot/index.asp
ניתן לקבלו מודפס ע"י פניה לחברת באייר ישראל, רח' החרש 36 הוד השרון, טלפון: 09-7626700.

בברכה,
באייר ישראל