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EMA restricts use of prostate cancer medicine Xofigo

Medicine to be used only after two previous treatments or when other treatments cannot be taken

The European Medicines Agency has concluded its review of the cancer medicine Xofigo (radium-223 dichloride), and has recommended restricting its use to patients who have had two previous treatments for metastatic prostate cancer (prostate cancer that has spread to the bone) or who cannot receive other treatments.

Xofigo must also not be used with the medicines Zytiga (abiraterone acetate) and the corticosteroid prednisone or prednisolone. Xofigo should not be used with other systemic cancer therapies, except for treatments to maintain reduced levels of male hormones (hormone therapy). The medicine should also not be used in patients who have no symptoms, in line with the current indication; in addition, the use of Xofigo is not recommended in patients with a low number of bone metastases called osteoblastic bone metastases.

The review of Xofigo was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) after data from a clinical study suggested that patients given Xofigo in combination with Zytiga and prednisone/prednisolone could be at risk of dying earlier and had more fractures than patients given placebo (a dummy treatment) with Zytiga and prednisone/prednisolone. The study included patients with no or only mild symptoms, whereas Xofigo is only authorised in patients with symptoms. In addition, the combination used in this study is now contraindicated. In the study, patients given the combination with Xofigo died on average 2.6 months earlier than those given the combination with placebo. In addition, 29% of patients who received the Xofigo combination had fractures, compared with 11% of patients given the placebo combination.

It is thought that Xofigo, which is taken up by the bone, accumulates at sites where the bone is already damaged, for example by osteoporosis or micro-fractures, increasing the risk of fracture. However, the reasons for a possible earlier death seen in this study are not fully understood. The company that markets Xofigo will have to conduct studies to further characterise these events and clarify the mechanisms behind them.

The PRAC's recommendations have now been endorsed by EMA's Committee for Medicinal Products for Human Use (CHMP) and will be sent to the European Commission for a final legal decision.



Information for patients

- The prostate cancer medicine Xofigo can increase the risk of having fractures. Also, having Xofigo together with the cancer medicine Zytiga and a corticosteroid medicine (prednisone or prednisolone) for prostate cancer could possibly increase the risk of death.
- Your doctor will not use the combination of Xofigo and the other two medicines for prostate cancer. In addition Xofigo, used on its own or with medicines called 'luteinising hormone releasing hormone (LHRH) analogues', will be reserved for patients who have had at least two previous treatments for prostate cancer that has spread to the bone, or who cannot receive other treatments.
- Xofigo is authorised for use only when the spreading cancer is causing symptoms; depending on how the cancer has spread to the bone, your doctor will decide whether Xofigo is the right treatment for you.
- Before, during, and after treatment with Xofigo your doctor will carry out tests to check the health status of your bones. Depending on the results of these tests, Xofigo may be interrupted or stopped, and you may be given an alternative treatment.
- Before starting and during treatment with Xofigo, your doctor may also give you a medicine to protect your bones from fractures.
- If you experience any new or unusual bone pain or swelling before, during or after your treatment with Xofigo, you should consult your doctor.
- If you have any questions or concerns about your treatment, speak to your doctor or pharmacist.

Information for healthcare professionals

- The use of Xofigo is associated with an increased risk of fractures. A possible increased risk of death was also observed in a clinical trial investigating Xofigo in combination with abiraterone acetate and prednisone/prednisolone in patients with asymptomatic or mildly symptomatic castration-resistant prostate cancer.
- Xofigo should only be used as monotherapy or in combination with an LHRH analogue for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, who are in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment.
- Xofigo is contraindicated in combination with abiraterone acetate and prednisone/prednisolone. In addition, Xofigo should not be started in the first 5 days following the last dose of abiraterone and prednisone/prednisolone. Subsequent systemic cancer treatment should not be initiated for at least 30 days after the last administration of Xofigo.
- Xofigo is not recommended in patients with a low level of osteoblastic bone metastases and in patients with only asymptomatic bone metastases. It is also not recommended in combination with systemic cancer therapies other than LHRH analogues.
- In mildly symptomatic patients, the benefit of treatment should be carefully assessed against its risks, considering that high osteoblastic activity is likely to be required for treatment benefit (see below for more information).

- Before starting and during treatment with Xofigo, an assessment of patients' bone status (e.g. by scintigraphy, bone mineral density measurement) and risk of fractures (e.g. osteoporosis, fewer than 6 bone metastases, medication increasing fracture risk, low body mass index) should be performed. Monitoring should continue for at least 24 months.
- In patients with a high baseline risk of fracture, carefully consider the benefit of treatment against the risks.
- Concurrent use of bisphosphonates or denosumab has been found to reduce the incidence of fractures in patients treated with Xofigo. Therefore such preventive measures should be considered before starting or resuming treatment with Xofigo.

The Agency's recommendations are based on the assessment of data from a randomised, double blind, placebo controlled phase III trial (ERA-223), which showed that there was an increased incidence of fractures (28.6% vs 11.4%), a possible reduction in median overall survival (30.7 months vs 33.3 months, HR 1.195, 95% confidence interval (CI) 0.950 - 1.505, p=0.13) and an increased risk of radiological non-bone progression (HR 1.376 [95% CIs 0.972, 1.948], p=0.07) among patients receiving Xofigo in combination with abiraterone acetate plus prednisone/prednisolone (n=401) compared to patients receiving placebo in combination with abiraterone acetate plus prednisone/prednisolone (n=405). An increased fracture risk was found particularly in patients with a medical history of osteoporosis and in patients with fewer than 6 bone metastases.

In another randomised, double blind, placebo controlled phase III trial (ALSYMPCA), a statistically significant overall survival benefit of treatment with Xofigo 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), indicating that efficacy may be diminished in patients with a low level of osteoblastic activity from their bone metastases.

More about the medicine

Xofigo is currently used to treat adult men with cancer of the prostate (a gland of the male reproductive system). It is authorised for use when medical or surgical castration (stopping the production of male hormones in the body using medicines or surgery) does not work, and when the cancer has spread to the bones and is causing symptoms such as pain but is not known to have spread to other internal organs.

Xofigo was authorised in the European Union in November 2013. More information on Xofigo is available on the EMA website: ema.europa.eu/Find_medicine/Human_medicines/European_public_assessment_reports

More about the procedure

The review of Xofigo was initiated on 1 December 2017 at the request of the European Commission, [Article 20 of Regulation \(EC\) No 726/2004](#).

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines. In March 2018, the

PRAC recommended contraindicating the use of Xofigo with Zytiga and prednisone/prednisolone, as an interim measure, while the review was ongoing.

The final PRAC recommendations were adopted on 12 July 2018 and then sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion. The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States in due course. The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.