Bayer HealthCare

23rd October 2014

# Direct HealthCare Professional Communication agreed by the CHMP on 16 Oct 2014

## ▼ Xofigo: temporary drug shortage

Dear Healthcare Professional,

Bayer Pharma AG in agreement with the European Medicines Agency and the Health Products Regulatory Agency (HPRA) would like to inform you of important information regarding drug shortage with potential impact on treatment decisions for Xofigo (radium Ra-223 dichloride), used in the treatment of castration-resistant prostate cancer.

**Summary**

- **Bayer is currently experiencing a worldwide temporary drug shortage for Xofigo® due to the failure of recent batches to pass routine pre-distribution quality checks.**
- **At this point in time Bayer is unable to anticipate when distribution of Xofigo® can be resumed.**
- **Patients who are currently on Xofigo will have to interrupt temporarily the treatment. Treating physicians should consider the need for switching to alternative therapies. The individual clinical situation of the patient should be taken into account in balancing risks and benefits of switching treatment.**
- **Until the product is available again, new patients cannot initiate treatment with Xofigo.**
- **Available data suggests that treatment interruption up to 4 weeks has no relevant impact on overall survival. There are no available data on the impact of delaying treatment for longer periods.**
- **Once the shortage has resolved, a resumption of treatment with Xofigo® may be considered.**

**Further information**

Recently produced Xofigo® drug product batches did not pass routine quality checks. These routine quality checks are in place to identify a quality issue before distribution occurs; product already released for distribution had passed these checks and was not affected. Bayer is taking the necessary actions to ensure high quality standards are restored and production can be quickly resumed.
These quality problems and the need for corrective action are resulting in a drug shortage. For patients on treatment the shortage may lead to therapy interruption. Until the product is available again, new patients cannot initiate treatment with Xofigo.

Given that there will be a treatment disruption, Bayer has examined available data from the Phase III ALSYMPCA study on treatment delays (ALpharadin in SYMptomatic Prostate CAncer; EudraCT number: 2007-006195-11; NCT00699751).

In the ALSYMPCA protocol, treatment delays for up to 4 weeks were allowed for patients who developed adverse events. The following advice was given with respect to delaying a dose in the study protocol:

> *"Study visits during the treatment period should occur at 4 weeks intervals (within a window of -3 days to +7 days). The same visit interval (4 weeks) applies between all treatments. If the window of -3 days to +7 days cannot be met, contact your Clinical Research Associate for advice. A study drug administration may be delayed by no more than 4 weeks for recovery of adverse events. In case of a treatment delay greater than 4 weeks, treatment should be discontinued."*

In an ad hoc analysis of this trial, ~30% (N=178/600) of patients had a delay in receiving radium-223. Of these 178 patients, 56 patients had delays caused by an adverse event and the remaining 122 patients had delays caused by other reasons.
The exposure to a full course (six injections) of radium-223 was similar regardless of whether patients experienced a delay, or not.
In addition, the impact of delayed administration of radium-223 on overall survival (OS) was analyzed. OS was 14.6 months median survival (95% CI 12.9-16.2) in patients with treatment delay in comparison with 15.3 months median survival (95% CI 13.9-16.8) in patients without treatment delay. The analysis suggests that delay of treatment for up to 4 weeks has no relevant impact on overall survival. However, these data need to be interpreted with caution as they are based on unplanned sub-group analyses.

Treating physicians should consider the need for switching to alternative therapies taking into account the clinical situation of the patient and balancing risks and benefits of treatment delay against risks and benefits of other available treatment options.

Bayer is in regular communications with physicians and investigators who treat patients with Xofigo® to provide information on product availability.

**Company contact point**
Contact point details for further information are given in the product information of the medicinal products (SmPC and PL) at: http://www.ema.europa.eu/ema/.

Yours sincerely,

Dr. Tristan P. Cooper MB BCh BAO FFPM
Medical Director

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for how to report adverse reactions.