1.1. Enzalutamide and difficulty swallowing the capsules

Introduction

Enzalutamide (Xtandi®) is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. It competitively inhibits binding of androgens to androgen receptors, inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression [1].
Enzalutamide is indicated for *the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated and for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy*.
Enzalutamide has been approved for the Dutch market since June 21st 2013 [1].

Enzalutamide is for oral use. It is a soft capsule, approximately 20 mm x 9 mm. The capsule should be swallowed whole with water. Patients should not chew or open the capsules. They can be taken with or without food. The recommended dose is 160 mg enzalutamide (four 40 mg capsules) as a single oral daily dose. Each soft capsule contains sorbitol (52.4 mg), caprylocaproyl macrogol-8 glycerides, butylhydroxyanisole (E320) and butylhydroxytoluene (E321) [1].

Reports

Between March 2015 and July 2016 Lareb received five reports of patients who had difficulty swallowing the enzalutamide capsules.

Case A (198941)
This is a case reported by a consumer referring to a patient 81-90 years who had problems swallowing the enzalutamide capsule because of the size. He had to take four capsules per day. The patient also experienced confusion, had shivers, urinary incontinence, cough, his throat filled with mucus which caused inability to drink, was hoarse and could not tolerate enzalutamide. He died four days after start of enzalutamide treatment.

Case B (222236)
This report from a consumer concerns a male aged 91-100 years, in whom the enzalutamide capsules were stuck in his throat after every administration. He also experienced cough. The complaints last for half an hour to several hours. The patient uses four capsules per day for prostate cancer. Concomitant medications were calcium/colecalciferol, paracetamol and prednisone.

Case C (210161)
This report from a pharmacist concerns a male aged 91-100 years, with sialorrhoea, dysphagia and esophageal stricture following administration of enzalutamide for prostate carcinoma. The dose for enzalutamide (four capsules per day) is not changed. The patient has not recovered. The reporter mentioned that the patient produces several teacups of saliva per day. The dysphagia means that the patient could not take solid food and could not properly swallow his medication. The patient experiences no pain during swallowing. Concomitant medications were buprenorphine, hydroxocobalamin, strontiumranelaat, prednisolone, omeprazole, glyceryl trinitrate, isosorbide mononitrate, calcium/colecalciferol, dutasteride, carbasalate calcium, atorvastatin, amlodipine and levothyroxine sodium.
The medical history indicates that the patient has angina pectoris, metastases to bone, hyperthyroidism and impaired liver function. The patient has no fever, influenza like symptoms, infection or a swollen throat.
After receiving follow-up the reporter mentioned that the patient had esophageal stenosis, probably due to metastases. The patient received a stent allowing to administer fluids and milled nutrition. It is unknown whether this helps in swallowing the enzalutamide capsules.

Case D (211600)
This is a case reported by a pharmacist referring to a male patient of unknown age who was not able to swallow enzalutamide every day due to swallowing difficulties from a stroke that happened five weeks earlier. Therefore the enzalutamide capsules were opened and the content was put in a cup to

drink it. He used four enzalutamide capsules per day for prostate cancer. Concomitant medications were calcium/colecalciferol, ranitidine, clopidogrel and ferrous fumarate.

Case E (220572)
This report from a specialist doctor concerns a male aged 61-70 years, with dysphagia following administration of enzalutamide. The patient had dysphagia complaints which improved after vomiting. The dose for enzalutamide is not changed. The patient recovered. Concomitant medications were goserelin and dutasteride.

Other sources of information

Literature
There are no case-reports about problems with swallowing the enzalutamide capsules published in the literature. However, there are articles published about older people having difficulties swallowing tablets and capsules. In a study by Liu et al they assessed acceptability of oral solid medicines in older ambulatory patients with and without dysphagia. They found that 60% of the participants without dysphagia deemed themselves having problems with swallowing any of the capsule sizes presented and 94% of participants with dysphagia. In participants with dysphagia 35% selected capsule size 00 as the size that would start to cause problems in swallowing [2].

Databases
September 20th 2016, the WHO database contains 357 cases of dysphagia associated with the use of enzalutamide and 211 cases of product size issue associated with the use of enzalutamide of which more than 90% are in combination with dysphagia [3].
October 4th 2016, the EudraVigilance database contains 211 cases of dysphagia associated with the use of enzalutamide and 96 cases of product size issue associated with the use of enzalutamide of which more than 90% are in combination with dysphagia [4].

Prescription data
The GIPdatabase does not contain prescription data about enzalutamide [5].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received five reports of patients who had difficulty swallowing enzalutamide capsules. We have no reason to believe that enzalutamide causes dysphagia, but the capsule size is the problem. The capsules have a diameter comparable with size 00 capsules which are the largest capsules in use for humans. The recommended dose is four capsules each day. In one report esophageal stenosis probably due to metastases complicated the case and in another report swallowing difficulties due to a stroke also played a role. One patient (case A), however, specifically mentioned that the size of the capsule is too big. The WHO and EudraVigilance database contain a lot of cases in which specifically product size issue is reported associated with the use of enzalutamide.
The 40 mg capsule of enzalutamide is the only formulation available, which causes a problem for some patients. We would therefore like to bring this to the attention of the MEB and the manufacturer.

References

1. Dutch SmPC enzalutamide. (version date: 28-4-2016, access date: 20-9-2016) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/002639/WC500144996.pdf
2. Liu F, Ghaffur A, Bains J, Hamdy S. Acceptability of oral solid medicines in older adults with and without dysphagia: A nested pilot validation questionnaire base observational study. Int J Pharm. 2016 Mar 9. pii: S0378-5173(16)30197-1. doi: 10.1016/j.ijpharm.2016.03.007. [Epub ahead of print]
3. WHO database Vigilyze. (dataset date: 14-9-2016, access date: 20-9-2016) https://vigilyze.who-umc.org/#/ (access restricted).
4. Eudravigilance database. (version v02.02.11, access date: 04-10-2016) http://bi.eudra.org (access restricted).
5. GIPdatabase - Drug Information System of the Dutch Health Care Insurance Board. (access date: 20-9-2016) http://www.gipdatabank.nl.

This signal has been raised on November 2016. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl