Abiraterone

Essential medicine status

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.4. Hormones and antihormones

ATC codes: L02BX03

Indication	Malignant neoplasms of prostate ICD11 code: 2D32.Z
INN	Abiraterone
Medicine type	Chemical agent
List type	Complementary
Formulations	Oral > Solid: 250 mg ; 500 mg
EML status history	First added in 2019 (TRS 1021)
Sex	Male
Age	Adolescents and adults
Therapeutic equivalence	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Tags	Cancer
Wikipedia	Abiraterone
DrugBank	Abiraterone

Expert Committee recommendation

The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration of abiraterone and enzalutamide. The Committee recommended the addition of abiraterone to the complementary list of the EML for use in the treatment of metastatic castrationresistant prostate cancer. The Expert Committee acknowledged the significant public health burden of prostate cancer, which afflicts an increasing number of people in all countries, irrespective of income. The Committee recalled that the EML currently includes docetaxel, bicalutamide and leuprorelin for use in the treatment of metastatic prostate cancer. However, a significant proportion of patients will not respond to these medicines and patients will ultimately develop resistance. The Committee noted that abiraterone and enzalutamide have each been shown to be effective treatments for metastatic castration-resistant prostate cancer, both in chemotherapy-naive and in pre-treated patients. The Committee noted that abiraterone had not shown any relevant clinical advantage over enzalutamide in terms of efficacy outcomes or safety. However, the Committee recognized the potential advantages offered by abiraterone in terms of emerging dosing strategies (lower doses may be possible when administered with food), reduced pill burden potentially improving adherence, wider availability of generics and potential associated cost savings. Given that metastatic prostate cancer often requires treatment over longer periods of time (i.e. above one year) and that low dosing and availability of generics would be associated with substantial cost savings, the Committee decided not to recommend listing abiraterone with a square box indicating enzalutamide as an alternative. While enzalutamide remains an effective therapeutic option for mCRPC, its use instead of abiraterone could result in considerable additional expenditure at country level, without additional clinical benefit. The Committee considered that addition of abiraterone alone on the EML serves to support its use, promoting competition between brand and generic medicines, and improving access and affordability.

Background

The application requested the addition of abiraterone and enzalutamide to the EML for use in the treatment of metastatic castration-resistant prostate cancer. In 2017, the Committee considered an application requesting inclusion of enzalutamide on the EML for the treatment of prostate cancer, but did not recommend inclusion, instead recommending a comprehensive review of prostate cancer medicines including abiraterone to be considered at its next meeting (1).

Public health relevance

Prostate cancer is the second most common cancer in men and the fourth most common cancer overall. In 2018, approximately 1.3 million men were diagnosed with prostate cancer (2). When patients are diagnosed with prostate cancer, if they are treated early and tumours are localized, the prognosis is often favourable. However, some patients will relapse, which in nearly all cases, leads to castrationresistant prostate cancer (CRPC). At the CRPC stage, the disease is no longer responsive to androgen deprivation therapy (ADT), thus limiting the available treatment options. There are currently six treatments being used to treat CRPC. Enzalutamide and abiraterone acetate have several advantages over the other treatments. Four of the other treatments are invasive and require IV administration, leukapheresis, or the use of radiopharmaceuticals. Enzalutamide and abiraterone acetate are the only daily oral tablets.

Benefits

Enzalutamide The application described the findings of two randomized placebo-controlled Phase III studies of enzalutamide for treatment of mCRPC. The AFFIRM trial randomly assigned 1199 men with metastatic CRPC (mCRPC) who had previously taken docetaxel to 160 mg enzalutamide or placebo daily (3). Both groups received continuing androgen deprivation therapy. Overall survival (OS) favoured enzalutamide (18.4 months vs 13.6 months; HR 0.63, 95%CI 0.53 to 0.75; p<0.001). Progression-free survival (PFS) also favoured enzalutamide (8.3 months vs 2.9 months; HR 0.40, 95%CI 0.35 to 0.47, p<0.001). 54% of enzalutamide-treated patients experienced a 50% or greater decrease in prostate specific antigen (PSA) levels compared to only 2% in the control arm (p<0.001). The PREVAIL trial investigated enzalutamide in a first-line setting in men with mCRPC who were chemotherapy naive. 1717 patients were randomized to receive 160 mg enzalutamide or placebo daily (4). The study was stopped after a planned interim analysis showed benefit for enzalutamide. Significantly fewer deaths were reported in the treatment arm compared to placebo (28% vs 35%; HR 0.71, 95%CI 0.60 to 0.84l p<0.001). Abiraterone acetate The application described the findings of two randomized placebo-controlled Phase III studies of abiraterone for treatment of mCRPC. The COU-AA-301 trial randomly assigned 1195 patients who had failed prior docetaxel therapy to receive prednisone 5 mg twice daily with either abiraterone 1000 mg daily or placebo (5). The primary endpoint was overall survival and was significantly longer in the abiraterone-prednisone arm compared to the control arm (14.8 months vs 10.9 months; HR 0.65, 95%CI 0.54 to 0.77; p<0.001). Abiraterone was also associated with significant benefit compared to placebo for the secondary endpoints of time to PSA progression (10.2 months vs 6.6 months; HR 0.58, 95%CI 0.46 to 0.73; p<0.001), and PFS (5.6 months vs 3.6 months; HR 0.67, 95%CI 0.59 to 0.78; p<0.001). The COU-AA-302 trial randomly assigned 1088 chemotherapy naive patients with prostate cancer to receive abiraterone 1000 mg daily plus prednisone 5 mg twice daily or placebo plus prednisone (6). Median overall survival was observed to be longer in abiraterone treated patients compared to the placebo group (34.7 months vs 30.3 months; HR 0.81, 95%CI 0.70 to 0.93; p=0.0033). Enzalutamide versus abiraterone acetate The application described the findings of three studies in which enzalutamide and abiraterone were compared. A network meta-analysis of eight RCTs involving 8666 patients with mCRPC compared the efficacy of abiraterone, enzalutamide and orteronel (7). Pooled hazard ratios for the primary endpoint of overall survival were 0.71 and 0.78 for enzalutamide and abiraterone, respectively compared to control groups. Enzalutamide also significantly improved PFS (HR 0.36), whereas abiraterone was not associated with a significant improvement. Enzalutamide and abiraterone were both associated with significant improvements in time to PSA progression compared to controls (HR 0.20 and 0.56, respectively). There were no significant associations for either drug with regard to the development of adverse events. A retrospective study of patients with mCRPC receiving treatment with enzalutamide (n=807) or abiraterone (n=2591) compared real-world treatment patterns and adherence to therapy (8). Abiraterone-treated patients were found to have higher medication possession ratios (MPRs) than enzalutamide-treated patients, suggesting greater medication adherence to abiraterone. Abirateronetreated patients also had lower Kaplan-Meier rates of dose reduction. A second retrospective study compared the combined duration of prostate cancer treatments of mCRPC patients initiated on abiraterone (n=2591) or enzalutamide (n=807)

(9). Compared with patients initiated on enzalutamide, patients initiated on abiraterone had fewer discontinuations of mCRPC treatments (HR 0.73, p=0.004) or of any prostate cancer treatments (HR 0.61, p=0.002) at three months and the result was maintained up to 24 months. The median duration of mCRPC treatments was 4.1 months longer for patients initiated on abiraterone compared with those initiated on enzalutamide (18.3 vs 14.2 months, p<0.001). Similarly, the median duration of any prostate cancer treatment was longer for patients initiated on abiraterone compared with those initiated on enzalutamide (not reached vs 22.2 months, p<0.001).

Harms

Enzalutamide From the PROSPECT trial in patients with non-metastatic disease, adverse events of Grade 3 or higher occurred in 31% of enzalutamide-treated patients compared with 23% receiving placebo. The most commonly reported adverse events occurring more frequently in the enzalutamide group included fatigue, hot flush, hypertension, nausea and constipation (10). From the AFFIRM trial in previously treated patients with mCRPC, adverse events of Grade 3 or above were reported in 45.3% of patients in the enzalutamide arm compared to 53.1% of placebo-treated patients. Enzalutamidetreated patients experienced a higher incidence of any grade fatigue, diarrhoea, hot flashes, musculoskeletal pain, headache and seizures compared to placebotreated patients. Adverse events causing death occurred in 3% and 4% of enzalutamide- and placebo-treated patients, respectively (3). From the PREVAIL trial in chemotherapy naive patients with mCRPC, adverse events of Grade 3 or more were reported in 43% of the patients in the enzalutamide group, and 37% in the placebo group. Common adverse events occurring at least 2% more frequently in the enzalutamide group included fatigue, back pain, constipation and arthralgia (4). Abiraterone In the COU-AA-301 trial, there were more deaths, treatment discontinuations, and treatment discontinuations due to adverse events in the placebo arm versus the abiraterone arm. Common adverse events occurring at similar frequency between treatment groups were fatigue, back pain, nausea, constipation, bone pain and arthralgia. Urinary tract infection was observed more frequently in the abiraterone arm (5). The most common Grade 3 or greater adverse events of special interest reported in the COU-AA-302 trial occurring more frequently in the abiraterone arm were cardiac disorders (8% vs 4%), increased alanine aminotransferase (6% vs <1%) and hypertension (5% vs 3%) (6).

Additional evidence

A recent prospective randomized Phase II study (n=72) investigated the effect of the administration of low dose abiraterone (250 mg daily) with a low-fat meal, compared to standard dose abiraterone (1000 mg daily) administered under fasting conditions (11). At 12 weeks, a greater effect on PSA was observed in the low-dose arm compared with the standard dose arm (mean log change −1.59 vs −1.19) meeting the predefined non-inferiority criteria. The PSA response rate was 58% and 50% in the low-dose and standard-dose arms, respectively. Median PFS was approximately nine months in both groups. Androgen levels decreased similarly in both arms. Abiraterone concentrations were higher in the standard-dose group, yet there was no difference in PSA response or PFS. The study authors considered these data could have significant pharmacoeconomic implications and deserve consideration by prescribers, payers and patients. However, the study also concludes that additional studies are required to determine the long-term efficacy of this dosing strategy.

Cost / cost effectiveness

Many of the cost-benefit studies have been done using the prices from originator companies. Both drugs are now also available from generic suppliers, and as competition among generic suppliers expands, prices should decline considerably. Before generic entry, some publicly quoted prices for the active pharmaceutical ingredient enzalutamide were in the range of US$ 6000 to US$ 13 000 per kg. At US$ 6000 per kg, the cost of the active pharmaceutical ingredient (API) for one 40 mg capsule of enzalutamide would be US$ 0.24 (US$ 0.006 per mg). Prices of generic abiraterone acetate vary. One company offers 120 x 250 mg abiraterone acetate tablets for approximately US$ 238.40. The price for a unit of the API is US$ 7947 per kg and US$ 0.007947 per mg. It is anticipated that API costs could decline to between US$ 300 and US$ 900 per kg over time for both products, in line with prices for tamoxifen (US$ 271 per kg), capecitabine (US$ 393 per kg) and prednisolone (US$ 962 per kg). A decline of that magnitude would result in API costs of US$ 0.012 to US$ 0.036 per 40 mg capsule, or US$ 0.048 to US$ 0.144 per day, for enzalutamide, and US$ 0.075 to US$ 0.225 per 250 mg tablet or US$ 0.30 to US$ 0.90 per day for abiraterone acetate (without prednisone). Technology appraisal guidance issued by the National Institute for Health and Care Excellence (NICE) for enzalutamide and abiraterone state that these medicines are recommended treatment options people with metastatic hormone-relapsed prostate cancer if the

manufacturers provide the drugs at agreed fixed or discounted prices (12, 13). Similarly, the National Centre for Pharmacoeconomics in Ireland approved reimbursement for enzalutamide and abiraterone only after price negotiations were conducted. The application summarized numerous studies that investigated the cost-effectiveness of enzalutamide and abiraterone, noting that many study authors were affiliated with the pharmaceutical manufacturers at the time of publication. The studies cited used the high originator prices and are of limited use when considering whether these medicines would be cost-effective in resource-limited settings, when and where the medicines available at lower prices from generic suppliers.

WHO guidelines

None available.

Availability

Enzalutamide and abiraterone acetate have worldwide regulatory approval. There are many generic versions of abiraterone acetate available, while only a single generic version of enzalutamide.

Other considerations

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it did not support the inclusion of abiraterone or enzalutamide on the EML for management of castration-resistant prostate cancer at this time, though noting with interest ongoing studies and more mature data that may demonstrate significant benefit, particularly for overall survival.

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13. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. Technology appraisal guidance [TA387]. London: National Institute for Health and Care Excellence; 2016. Available from https://www.nice.org.uk/guidance/ta387, accessed 29 September 2019.