Fulvestrant
The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.
Rejected
Section:
8. Immunomodulators and antineoplastics 8.2. Antineoplastics and supportive medicines 8.2.4. Hormones and antihormones
ATC codes: L02BA03
Indication
Malignant neoplasms of breast ICD11 code: 2D2Z
INN
Fulvestrant
Medicine type
Chemical agent
List type
Complementary
Formulations
Parenteral > General injections > IV: 250 mg per 5 mL
EML status history
Application rejected in 2021 (TRS 1035)
Sex
All
Age
Adolescents and adults
Therapeutic alternatives
The recommendation is for this specific medicine
Patent information
Patents have expired in most jurisdictions
Read more about patents.
Tags
Cancer
Wikipedia
Fulvestrant
DrugBank
Fulvestrant
Expert Committee recommendation
☐
The Expert Committee considered that it was difficult to come to any definitive conclusion about the superiority of fulvestrant in combination with aromatase inhibitors compared with aromatase inhibitors alone. The studies included in the meta-analysis had heterogeneous results. The cumulative median overall survival gain of 7 months and median progression-free survival gain of 1 month for fulvestrant were based on low-certainty evidence. The Committee also noted that the price of fulvestrant is very high in most settings and its cost–effectiveness is unclear. The Committee therefore did not recommend adding fulvestrant to the EML at this time because of uncertainty in the estimates of survival benefit.
Background
☐
Fulvestrant has not previously been considered for inclusion on the EML. In 2015, as part of a comprehensive review of cancer medicines on the EML, the following medicines were endorsed for inclusion on the EML for use in protocols for the treatment of metastatic breast cancer: capecitabine, cyclophosphamide, docetaxel, doxorubicin, paclitaxel, vinorelbine, anastrozole and tamoxifen. Trastuzumab was also recommended for treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage and metastatic breast cancer (1).
Public health relevance
☐
Breast cancer is the most frequent malignant disease in women. The estimated number of new cases in 2020 was 2 261 419, accounting for 25% of all cancers in women. The global age-standardized incidence rate is 47.8/100 000 people, with the highest rate observed in Australia and New Zealand (95.5/100 000 people). Incidence is much lower in Africa and Asia (< 50/100 000 people). The global age-standardized mortality rate is 13.6 per 100 000, ranging from 9.8 per 100 000 in Eastern Asia to 27.5 per 100 000 in Melanesia (2). Many women initially diagnosed in early stages will progress to a metastatic stage. It has been estimated that only 25% of the women living with metastatic breast cancer are new cases, while 75% being recurrences of previously localized disease (3). While improved early detection and advances in systemic therapy for the early-stage disease have resulted in some decline in breast cancer mortality since 1989, metastatic breast cancer remains largely incurable with a median survival of about 24 months (4). Factors associated with poor survival include age ≥ 50 years, visceral disease, shorter disease-free interval, aneuploid tumours, tumours with a high S-phase fraction, p53 accumulation, low BCL-2 expression, negative hormone receptor status, and positive HER2 status (5).
Benefits
☐
The applicants conducted a literature search for randomized trials and systematic reviews of fulvestrant plus aromatase inhibitors in women with metastatic breast cancer, and conducted a meta-analysis of the results. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias Tool, and judgements about precision, consistency, directness and likelihood of publication bias were made following the GRADE approach. Six systematic reviews (6–11) (used to identify relevant studies) and three randomized trials (12–14) were identified. Two trials reported data to estimate the effect on overall survival and were included in the meta-analysis (12,13). The open-label, phase III FACT trial was conducted in premenopausal women receiving a gonadotropin-releasing hormone agonist and postmenopausal women,

both groups with hormone-receptor-positive breast cancer who had relapsed after primary treatment (12). A total of 514 participants were randomized 1:1 to receive a loading dose of fulvestrant followed by monthly fulvestrant plus daily anastrozole (n = 258) or daily anastrozole alone (n = 256). No difference in median overall survival was observed (37.8 versus 38.2 months; hazard ratio (HR) 1.0, 95% confidence interval (CI) 0.76 to 1.32). The phase III SWOG0266 trial was conducted in postmenopausal women with previously untreated hormone-receptor-positive metastatic breast cancer (13). A total of 707 participants were randomized 1:1 to receive a loading dose followed by monthly fulvestrant plus daily anastrozole (n = 350) or daily anastrozole alone (n = 345). After a median follow-up of 35 months, median progression-free survival was 15.0 months in the fulvestrant plus anastrozole arm versus 13.5 months in the anastrozole arm (HR for progression or death with combination therapy 0.80, 95% CI 0.68 to 0.94). The results of the meta-analysis did not show a statistically significant survival benefit for fulvestrant, but the point estimate for overall survival was in favour of the combination of fulvestrant plus aromatase inhibitors (HR 0.85, 95% CI 0.62 to 1.15, corresponding to an overall survival benefit of the combination of about 7 months in absolute terms; low-certainty evidence). There was low-certainty evidence that fulvestrant plus aromatase inhibitors might increase progression-free survival by 1 month compared to aromatase inhibitors (HR 0.89, 95% CI 0.73 to 1.08; low-certainty evidence). Substantial heterogeneity was seen between the studies in the meta-analysis, with the FACT trial suggesting no effect and the SWOG0226 trials showing a benefit for fulvestrant. The disparity may be explained by the important difference in the type of patients included (pretreated versus treatment-naïve patients and percentage of patients with distant metastases).

Harms

Three trials provided data on adverse events and were included in the meta-analysis (12,13,15). The results found moderate-certainty evidence that treatment with fulvestrant plus anastrozole may or may not increase the risk of adverse events compared with treatment with anastrozole alone (risk ratio (RR) 1.03, 95% CI 0.92 to 1.15). In absolute terms, 15 more patients per 1000 patients treated might experience adverse events of grade 3 or higher with the combination therapy, but the confidence intervals are wide (from 26 fewer to 59 more). The most commonly reported adverse events were gastrointestinal disorders, hot flashes, headache, arthralgia and bone pain.

Additional evidence

Overall survival data from the SWOG0266 trial were reported after a median follow-up of 7 years in patients who did not have disease progression (16). Median overall survival was 49.8 months in the combination therapy group versus 42.0 months in the anastrozole group (HR for death 0.82, 95% CI 0.69 to 0.98). In the subgroup of patients who had not previously received endocrine therapy, median overall survival was 52.2 months in the combination therapy group versus 40.3 months in the anastrozole monotherapy group (HR for death 0.73, 95% CI 0.58 to 0.92). The selective crossover from the anastrozole alone group to the combination was about 45%. These data were not included in the meta-analysis conducted by the applicants.

Cost / cost effectiveness

The applicants identified two cost–utility analyses that evaluated the cost–effectiveness of fulvestrant (17,18). A study in China compared half-dose fulvestrant plus anastrozole against full-dose fulvestrant monotherapy and anastrozole monotherapy as first-line treatment for hormone-receptor-positive metastatic breast cancer (17). The study used clinical input data from the SWOG0266 trial (16) and from a phase II randomized trial comparing fulvestrant monotherapy with anastrozole monotherapy (19). Compared with anastrozole monotherapy, combination half-dose fulvestrant plus anastrozole was a cost-effective alternative as the incremental cost–effectiveness ratio was US$ 15 666 per quality adjusted life year (QALY) gained, less than the willingness-to-pay threshold of US$ 29 383 in China. Another cost–effectiveness analysis assessed fulvestrant plus anastrozole compared with anastrozole alone as first-line therapy in women with hormone-receptor-positive metastatic breast cancer from an American payer’s perspective (18). The analysis used clinical input data from the SWOG0266 trial (16). The combination of fulvestrant plus anastrozole showed an incremental cost–effectiveness ratio of US$ 300 564 per QALY gained for all eligible patients and of US$ 194 450 per QALY gained for patients without previous hormonal adjuvant therapy. Applying a willingness-to-pay threshold of US$ 150 000, addition of fulvestrant to breast cancer treatment was not considered to be cost-effective compared with anastrozole. Coverage recommendations for fulvestrant from national reimbursement agencies vary. In Australia and Canada, reimbursement for fulvestrant has been recommended for the treatment of postmenopausal women with hormone-receptor-positive and HER2-negative unresectable advanced or metastatic breast cancer. However, reimbursement in the United Kingdom of Great Britain and Northern Ireland has not been recommended.

WHO guidelines

WHO guidelines for the treatment of breast cancer are not available.

Availability

Fulvestrant has marketing approval from multiple national regulatory agencies, including the Australian Therapeutic Goods Administration, the European Medicines Agency, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency and the United States Food and Drug Administration. It is available in branded and generic forms.

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of fulvestrant on the EML for the treatment of metastatic breast cancer. The Working Group noted that available data on the use of fulvestrant in first-line treatment are not yet conclusive, while its use in second-line treatment is more established and data are more mature. The meta-analysis presented in the application did not differentiate between first- and second-line use. From the meta-analysis presented, the overall survival benefit for fulvestrant (plus aromatase inhibitor) was modest but meets the threshold of survival gain endorsed by the Expert Committee. However, there was substantial heterogeneity between the included trials, postprogression therapies were unclear and the benefit not accepted unequivocally. The Working Group also noted that the high cost of fulvestrant, the large potentially eligible patient population and variable findings in cost–effectiveness analyses were further limitations. Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that there is insufficient evidence of significant clinical effect of fulvestrant in comparison to medicines already included in the EML.

☐ Show references Hide references
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