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Date of Request: August 28, 2017

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for "Breast Cancer" to review the enclosed data for inclusion of FASLODEX® (fulvestrant) as a monotherapy option for the treatment of hormone receptor (HR)-positive, human epidermal growth receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy. This request is based on the recent Food and Drug Administration (FDA) approval of fulvestrant for this indication on August 25, 2017.[1] Please see the new Prescribing Information brochure (attached), as well as the information below which was previously submitted for the August 4, 2017 Breast Cancer Panel Meeting.

Specific Changes:

- We respectfully request addition of fulvestrant to the Breast Cancer guidelines as a monotherapy option for the treatment of HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.

FDA Status:

- Fulvestrant was approved on August 25, 2017 by the FDA as a monotherapy option for the treatment of hormone receptor (HR)-positive, human epidermal growth receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.
- Fulvestrant is also indicated for the:
  - Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
  - Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

Rationale:

- Fulvestrant is now indicated for use in this patient population.
- In the Phase III, randomized, double-bind FALCON trial, fulvestrant 500 mg demonstrated a significant improvement in PFS compared with anastrozole 1 mg [16.6 months vs. 13.8 months; HR 0.797 (95% CI 0.637, 0.999); p=0.0486] when given in the first line setting to endocrine therapy-naïve postmenopausal women with HR+ advanced breast cancer.[2] These results confirmed the clinical benefit of fulvestrant versus anastrazole seen in the FIRST trial.[3,4]
- The Phase II, FIRST trial compared fulvestrant 500 mg with anastrozole 1 mg daily as first-line endocrine therapy in postmenopausal women with advanced HR+ breast cancer. In the primary analysis, clinical benefit rate (CBR) and objective response rate (ORR) did not significantly differ between groups.[3] In both the primary analysis and an updated analysis, time to progression (TTP) was significantly improved with fulvestrant.[4] In another analysis, conducted after 66.8% of patients had died, overall survival (OS) was significantly improved with fulvestrant compared to anastrazole (54.1 months vs. 48.4 months; HR 0.70 (95% CI 0.50, 0.98); p=0.04].[5]

Reference(s): The following references are submitted in support of this proposal. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. FASLODEX Prescribing Information.
2. Robertson JF, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrazole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *Lancet.* 2016;388:2997–3005.
3. Robertson JFR, Llombart-Cussac A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-lime treatment for advanced breast cancer: results from the FIRST study. *J Clin Oncol.* 2009;27:4530-4535.
4. Robertson JFR, Lindemann JPO, Llombart-Cussac A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. *Breast Cancer Res Treat*. 2012;136:503-511.
5. Ellis MJ, Llombart-Cussac A, Feltl D, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: overall survival analysis from the phase II first study. *J Clin Oncol*. 2015;33:3781-3786.

Sincerely,

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