

June 30, 2014

**Subject: NCCN Breast Cancer Treatment Guidelines – Submission Request**

On behalf of DARA BioSciences, Inc., I respectfully request the NCCN Breast Cancer Clinical Practice Guidelines Panel to review the enclosed data in support of including tamoxifen citrate oral solution as an option to tamoxifen tablets in the management of breast cancer.

**Specific Changes:** Include the recommendation “Consider offering the option of a liquid formulation of tamoxifen to those patients who prefer or need a liquid formulation” as a footnote to the 5<sup>th</sup> bullet on page BINV-16 that reads “assess and encourage adherence to adjuvant endocrine therapy” as a strategy to support long term adherence to therapy.

**FDA Clearance:** The FDA-approved 505 (b) (2) liquid formulation of tamoxifen citrate (Soltamox®) is bioequivalent to the tablet formulation; the labels for the two formulations are essentially identical.<sup>1</sup>

**Rationale:** Due to a compelling need to improve patient adherence to long-term tamoxifen therapy, a liquid formulation is an important therapeutic option for specific populations, notably patients who have either physiological or psychological difficulties swallowing tablets and those who prefer an oral solution.

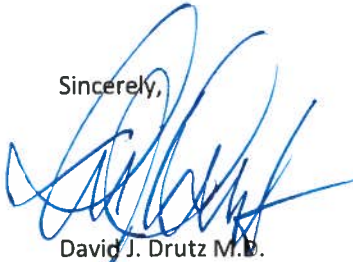
**Support for Recommendation:**

- Adherence to adjuvant tamoxifen hormonal therapy among breast cancer patients is poor, with 15-20% discontinuing therapy during the first year, increasing to 31-60% discontinuance at the end of year 5.<sup>2,3</sup> With current NCCN Breast Cancer Guidelines indicating physicians “consider tamoxifen for an additional 5 y to complete 10 y” (BINV-J), adherence is likely to become even more problematic.
- At the NCCN 2014 Annual Meeting, Professor Stefan Glück presented data from an IRB-approved 626 patient survey of female breast cancer patients regarding adherence to tamoxifen tablets and potential strategies to improve long-term adherence to the medication.<sup>4</sup>
  - Consistent with the literature, adherence was shown to be an issue, with 14% of patients self-reporting missing 2 or more tamoxifen doses each month.
  - 13% of patients indicated a preference for a liquid tamoxifen formulation; liquid formulation willingness/preference was higher in patients with lower self-reported adherence and/or swallowing difficulties.
  - 22% of patients indicated a willingness to try a liquid formulation.
  - Based on a validated, symptom specific outcome instrument for swallowing difficulties called the EAT-10,<sup>5</sup> the prevalence of swallowing difficulties in patients taking tamoxifen tablets was 8%.
- Dysphagia<sup>6</sup>, although only peripherally addressed in current NCCN guidelines [Version 2.2014 – Special Considerations for Patients Able to Tolerate Treatment – Senior Adult Oncology (SAO-4); Version 2.2014 – Principles of Nutrition: Management and Supportive Care – Head and Neck Cancers (NUTR-A)] is a potentially important issue with regard to adherence to oral medication, especially among the elderly. Rather than crushing pills into food, which is not advisable<sup>7</sup>, a liquid formulation of tamoxifen offers an alternative means of delivering the medication in a dose-accurate manner.

The following references are submitted in support of this proposed change.

1. Soltamox<sup>®</sup> (tamoxifen citrate) Oral Solution and tamoxifen tablet Package Inserts.
2. Murphy CC, et al. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. Breast Cancer Res Treat. 2012, 134(2): 459–478. DOI: 10.1007/s10549-012-2114-5.
3. Owusu C, et al. Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer. J Clin Oncol 2008, 26:549-555.
4. Glück et al. CAPTURE (Compliance and Preference for Tamoxifen Registry) Patient Survey Reveals Potential Strategies to Improve Long-Term Adherence to TAM Based on Choice: Results of a Large Internet-Based Survey. Journal of the National Comprehensive Cancer Network 2014, Volume 12 (4):455-456. Abstract and Poster.
5. Belafsky P, et al., Validity and Reliability of the Eating Assessment Tool (EAT-10) Ann Otol, Rhinol Laryngol. 2008, 117: 919-924
6. Raber-Durlacher JE, et al. Swallowing dysfunction in cancer patients. Support Care Cancer 2012, 20: 433-443.
7. Jackson LD, et al. Safe medication swallowing in dysphagia: a collaborative improvement project. Healthcare Quarterly 2008, 11: 110-116.

Sincerely,



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