**NCCN Adjuvant Breast Cancer Submission Cover Letter**

Date: June 17, 2014

Submission Request c/o Joan McClure
National Comprehensive Cancer Network
500 Old York Road, Suite 250
Jenkintown, PA 19046

**RE: Clinical Evidence in Support of the Use of Toremifene for Breast Cancer in the Adjuvant Setting**

Name: Deborah Braccia, PhD, MPA
Company/Organization: ProStrakan Inc
Address: 685 Route 202/206, Bridgewater, NJ 08807
Phone: 908-432-7271
E-mail: Deborah.Braccia@prostrakan.com

Date of request: June 17, 2014
NCCN Guidelines Panel: Breast Cancer

Dear Guidelines Panel,

On behalf of ProStrakan Group, I respectfully request the NCCN Breast Cancer Guidelines Panel to review the enclosed data for the use of toremifene citrate (Fareston®) in the adjuvant management of patients with hormone-receptor–positive breast cancer.

**Specific changes**: As a result of the information provided in this letter and the accompanying documentation, we are requesting a change to the adjuvant endocrine therapy section of the guidelines (BINV-J).

We are also requesting an expansion of the footnote in the adjuvant treatment algorithm and discussion section to include information regarding the lack of interaction of toremifene with CYP2D6 inhibitors such as selective serotonin reuptake inhibitors (SSRIs) and to specify that patients taking concomitant medications that inhibit cytochrome P-450 2D6 (CYP2D6) may consider toremifene when clinically appropriate.

**FDA status**: Fareston® (toremifene citrate) has not been approved in the United States for adjuvant treatment of patients with breast cancer.

**Rationale for recommended changes**: Although they have similar efficacy and safety profiles, an important differentiation between tamoxifen and toremifene lies in the clinical role of their respective metabolites, and this difference may impact treatment decisions. Specifically, there are data demonstrating that potent CYP2D6 inhibitors, such as common SSRIs, may affect the metabolism of tamoxifen but not that of toremifene. As a result, an alternative SERM to tamoxifen is needed for early breast cancer patients who have attained clinical success with certain SSRIs and do not wish to change antidepressants.

The efficacy and safety of toremifene in the adjuvant setting have been demonstrated in several published prospective studies totaling over 7,500 patient-years' experience with toremifene. We

believe this body of evidence in head-to-head, randomized controlled trials demonstrating noninferiority compared to tamoxifen represents a high level of evidence of toremifene's efficacy and safety in this setting.

**Supporting literature**: This request to amend the NCCN treatment guidelines to include toremifene as an option for the adjuvant treatment of estrogen-receptor–positive/progesterone-receptor–positive breast cancer is based on several key studies that are briefly described in the accompanying synopsis (the full list of supporting articles is in the synopsis document).


1. Gu R, Jia W, Zeng Y, et al. A comparison of survival outcomes and side effects of toremifene or tamoxifen therapy in premenopausal estrogen and progesterone receptor positive breast cancer patients: a retrospective cohort study. *BMC Cancer*. 2012;12:161.
2. Qin T, Yuan ZY, Peng RJ, Zeng YD, Shi YX, Teng XY, et al. Efficacy and tolerability of toremifene and tamoxifen therapy in premenopausal patients with operable breast cancer: a retrospective analysis. Curr Oncol 2013;20(4):196-204.
3. Holli K, Valavaara R, Blanco G, et al. Safety and efficacy results of a randomized trial comparing adjuvant toremifene and tamoxifen in postmenopausal patients with node-positive breast cancer. Finnish Breast Cancer Group. *J Clin Oncol.* 2000;18(20):3487-3494.
4. International Breast Cancer Study Group, Pagani O, Gelber S, et al. Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93. *Ann Oncol.* 2004;15(12):1749-1759.
5. Kim J, Dalton JT, Veverka KA. Relationship of CYP2D6 status and toremifene metabolism. *J Clin Oncol.* 2011; 29(suppl); abstract e13068.
6. Kim J, Coss CC, Barrett CM, et al. Role and pharmacologic significance of cytochrome P-450 2D6 in oxidative metabolism of toremifene and tamoxifen. *Int J Cancer*. 2013;132(6):1475-1485.
7. Kimura M, Tominaga T, Kimijima I, et al. Phase III randomized trial of toremifene versus tamoxifen for Japanese postmenopausal patients with early breast cancer. *Breast Cancer*. 2012 Sep 12.
8. Lewis JD, Chagpar AB, Shaughnessy EA, Nurko J, McMasters K, Edwards MJ. Excellent outcomes with adjuvant toremifene or tamoxifen in early stage breast cancer. *Cancer*. 2010;116(10):2307-2315.


We appreciate the opportunity to provide this additional information for consideration by the NCCN Breast Cancer Panel. If you have any questions or require additional information, please do not hesitate to contact me at 908-432-7271 or via e-mail at deborah.braccia@prostrakan.com. Thank you for your time and consideration.

Sincerely,

Deborah Braccia, PhD, MPA

Enclosures:
Table of proposed changes
Synopsis
Copies of referenced literature


ProStrakan, Inc
685 Route 202/206, Suite 101
Bridgewater, New Jersey 08807
Tel: 908 234 1096 Fax: 908 234 2835