DRAFT

QUESTIONS FOR THE ODAC
SNDA 20726 FEMARA (LETROZOLE)
DECEMBER 13, 2000

PROPOSED INDICATION "first-line therapy in postmenopausal women with advanced breast cancer"

One randomized controlled double-blind multinational clinical trial was conducted in 916 postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer comparing Femara 2.5 mg orally once daily with Tamoxifen 20 mg orally once daily. The safety and efficacy data are shown in the following Tables.

Table 1 Efficacy Results per Novartis and per FDA

	Novartis			**FDA**		
	Femara 453 pts	Tam 454 pts	p	Femara 456 pts	Tam 456 pts	p
Response Rate						
CR	34 (8%)	13 (3%)		39 (9%)	14 (3%)	
PR	103 (23%)	79 (17%)	0.0006[1]	108 (24%)	84 (18%)	0.0003[1]
Total	137 (30%)	92 (20%)		147 (32%)	98 (21%)	
Resp Duration (mo)	17.0	16.5	NS	11.5	10.3	0.94
Median TTP (mo)	9.4	6.0	0.0001[2]	9.87	6.15	0.0001[2]

[1] Chi Square Test, Two-Sided

[2] Log Rank Test, Two-Sided

Table 2 Serious AE's per FDA

Toxicity	Femara (455 pts)	Tamoxifen (455 pts)
Peripheral thromboembolic events	8 (2%)	11 (2%)
Cardiovascular events	7 (2%)	4 (1%)
Cerebrovascular events	5 (1%)	6 (2%)
Fractures	21 (5%)	18 (4%)
Endometrial cancer	0 (0%)	1 (0.2%)
Ocular toxicity	7 (2%)	5 (1%)
Hot flashes	82 (18%)	72 (16%)
Vaginal discomfort	12 (3%)	9 (2%)
Decreased WBC's or platelets	3 (0.7%)	0 (0%)

- Peripheral thromboembolic events included venous thrombosis, thrombophlebitis, portal vein thrombosis and pulmonary embolism.
- Cardiovascular events included angina, myocardial infarction, myocardial ischemia, and coronary heart disease.
- Cerebrovascular events included transient ischemic attacks, thrombotic or hemorrhagic strokes and development of hemiparesis.
- Fractures- 21 Femara treated patients had a total of 26 fractures compared 18 tamoxifen treated patients who had a total of 20 fractures. All, or almost all, fractures were disease-related.

At the June 1999 meeting the Committee indicated that for approval of new cytotoxic drugs for initial treatment of metastatic breast cancer a favorable effect on survival in randomized controlled trials is required. The Committee indicated that a favorable effect on time to tumor progression (TTP) is not adequate for approval. An impressive improvement of TTP in the range of 4-6 months would be adequate for accelerated approval. A better tumor response rate is not adequate for approval.

The rationale is that most cytotoxic drugs have significant toxicity. TTP and tumor response rate are not shown to be surrogates for survival. Usually only a minority of patients have a tumor response and most of these are partial

responses. TTP effects are usually modest. In the absence of a favorable effect on survival it is not clear that a better TTP or tumor response rate is sufficient to overcome the drug toxicity.

In contrast the FDA has accepted a favorable effect on tumor response or TTP in randomized controlled trials as adequate for approval of hormonal drugs for initial treatment of metastatic breast cancer. Demonstration of statistical superiority or non-inferiority of survival is not required, but updated survival data are required at the time of approval. If survival is trending strongly against the new hormonal drug, a decision on approval will be delayed until more mature survival data are available. Mature survival data are not usually available when Marketing Applications for hormonal drugs are initially submitted to the FDA.

The rationale is that hormonal drugs have modest toxicity relative to cytotoxic drugs. A favorable effect on tumor response rate or TTP comes at a lesser cost in toxicity than with cytotoxic drugs.

1. Does the Committee agree with the FDA's criteria for approval of hormonal drugs for initial treatment of advanced metastatic breast cancer?

2. Is Femara effective for initial hormonal treatment of locally advanced or metastatic breast cancer?

3. In view of the efficacy is the safety of Femara adequate ?

4. Is the Femara SNDA approvable?