Questions to the Committee

December 13, 2000

NDA 20-726/S-006 **Femara® (letrozole) Tablets**
Novartis Pharmaceuticals Corporation

Indication: first-line therapy in postmenopausal women with advanced breast cancer

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One randomized controlled double-blind multinational clinical trial was conducted in 916 postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced (Stage IIIB or locoregional recurrent disease not amenable to treatment with surgery or radiation) or advanced 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 453 pts	Tam 454 pts	p
Response Rate						
CR	34 (8%)	13 (3%)		39 (9%)	14 (3%)	
PR	103 (23%)	79 (17%)		108 (24%)	84 (18%)	
Total	137 (30%)	92 (20%)	0.0006[1]	147 (32%)	98 (21%)	0.0003[1]
Resp Duration (mo)	17.0	16.5	Not Done	11.5	10.3	Not Done
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%)

- 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 advanced 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 in TTP may be adequate for accelerated approval. A modest improvement in TTP, even if statistically significant, would not be adequate for accelerated approval. A better tumor response rate is not adequate for approval.

The rationale is that cytotoxic drugs have been shown to increase survival. TTP and tumor response rate are not shown to be surrogates for survival. Also cytotoxic drugs usually have significant toxicity. 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 advanced metastatic breast cancer. Updated survival data are required at the

time of approval, but demonstration of statistical superiority or non-inferiority of survival is not required. 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. In addition, hormonal drugs have not been shown to increase survival in this setting. Non-inferiority of survival in this setting is considered a safety endpoint and is not an indication of efficacy. If a new hormonal drug is shown to increase survival, the FDA will probably require future new hormonal drugs to demonstrate a favorable effect on survival to gain marketing approval.

Questions to the Committee

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

2. Does the single study comparing Femara with Tamoxifen show that Femara is effective for initial hormonal treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown advanced metastatic breast cancer?

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

4. Is the Femara sNDA approvable?