FDA Intrinsa Advisory Committee Background Document Overview
December 2, 2004

Introduction

Proctor and Gamble submitted NDA 21-769 on June 21, 2004 for Intrinsa, testosterone transdermal system (TTS), for the following proposed indication:

"Treatment of hypoactive sexual desire disorder in surgically menopausal women receiving concomitant estrogen therapy. Hypoactive sexual desire disorder (HSDD) is the persistent or recurrent deficiency or absence of sexual thoughts, fantasies, and/or desire for or receptivity for sexual activity, which causes personal distress or interpersonal difficulties. Low sexual desire may be associated with low sexual activity, sexual arousal problems or orgasm difficulty."

The proposed dosing regimen is one TTS 300 mcg patch applied twice weekly on a continuous basis.

There is no product approved for this indication in the United States, and the Applicant undertook clinical development of this product following the FDA's Draft Guidance on Female Sexual Dysfunction, which stresses the importance of using validated instruments for assessing responses to FSD therapy in specific target populations. The Applicant developed 3 psychometric instruments for use in the studies to assess the efficacy of TTS in treatment of HSDD in surgically menopausal women. The clinical program included two blinded, placebo-controlled Phase 3 studies (2001133 and 2001134) that each enrolled over 500 women. These studies were conducted in the US, Canada, Europe and Australia with more than 90% of the subjects from the US. The safety data base includes data from

a. A 24-week double blind placebo controlled phase permitting prospective safety comparisons that enrolled 696 women into the TTS group,
b. A 28-week open label phase which enrolled 837 women who were exposed to TTS (of which 418 previously were on the placebo control arm of the double blind phase and 419 were TTS-treated and thus were exposed to TTS for up to a total of 52 weeks),
c. An open label on-going 3-year safety extension phase (with data through 26-weeks of treatment) that enrolled 321 women from the 28-week open label phase. Of these women, 167 previously had been exposed to TTS for 28 weeks and 154 previously had been exposed to TTS for 52 weeks.

Points to Consider

The major issues that the FDA would like the Advisory Committee for Reproductive Health Drugs to consider include:

1) **Clinical Meaningfulness of the Efficacy Results**. Although both of the two major Phase 3 double blind, placebo controlled trials supporting this application found TTS to be statistically significantly superior to placebo in the primary and two major secondary endpoints studied, it is not clear that the differences identified are clinically meaningful. For example, for the primary endpoint of

change in number of satisfying sexual events from baseline, the mean observed difference between the increase in the TTS arm and the increase in the placebo arm was an approximate difference of one more event per 4 weeks in the TTS arm.

2. **Long Term Safety Concerns.** The demonstrated efficacy and its clinical significance must be considered in light of both demonstrated and potential risks associated with long term concomitant use of estrogen and testosterone. The unexpected safety findings from the Women's Health Initiative (WHI) studies on the risks and benefits of estrogen and combined estrogen and progestin in postmenopausal women indicated that short-term or uncontrolled studies may not provide adequate estimates of the risks of hormonal therapy. The data from the WHI studies are particularly relevant to making a risk/benefit assessment for TTS, because the women for whom this product will be indicated will also be taking estrogen. The WHI estrogen-only study data from women status post hysterectomy showed that treatment with equine estrogen increased the risk of cerebrovascular events. If this NDA is approved, another hormone, testosterone, will be added to estrogen. In the second WHI study, the addition of progesterone to estrogen increased the risk of breast cancer and adverse cardiovascular effects. It is unknown whether the addition of a different hormone, testosterone, might have similar and unanticipated adverse effects that have not been demonstrated in the Applicant's safety data base that presently includes only a very small number of subjects who have been treated beyond one year.

.

3. **Long Term Safety Assessment.** FDA asks that the Advisory Committee for Reproductive Health Drugs consider whether there are unanswered safety questions that should be further assessed pre-approval in appropriately sized randomized trials of adequate duration, or whether these questions can appropriately be answered post-approval. Proctor and Gamble has proposed a post-marketing pharmacovigilance plan that focuses on a cohort study conducted in a claims-based database to address questions regarding the potential long term safety of TTS use. Should the Committee decide that the efficacy and safety data presented at this meeting support approval of the product, the FDA would like the Committee members to consider whether the Applicant's pharmacovigilance plan is adequate to address unanswered questions about long term safety. Background rates of events of potential interest and time course of these events in women of this age group should be factored into these considerations, as well as the merit and feasibility of conducting trials of alternative designs (e.g., randomized controlled trials) in the population of interest.