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Quick Pulse

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THE FDA'S ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS REJECTS PROCTER & GAMBLE'S INTRINSA PATCH

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December 2, 2004

An FDA advisory committee unanimously recommended against approval of Procter & Gamble's TTS (Testosterone Transdermal System) patch, Intrinsa, until more safety studies are done. The FDA is expected to make a decision on the patch in the next few weeks. P&G is seeking approval of the patch for treatment of HSDD (hypoactive sexual desire disorder) in surgically menopausal women on concomitant estrogen. The patch delivers 300 µg of testosterone daily when applied twice a week as continuous therapy.

Although the panel gave thumbs down to Intrinsa for now, it said P&G should work with the FDA to come up with better safety studies. Thus, it appears most likely that the FDA will give P&G an approvable letter for Intrinsa, with a request for additional data, and it may take time for P&G to collect all the required data. The panel suggested P&G should have to:

- Study more women (one panelist recommended at least 5,000) to see if the hormone patch unacceptably increases the risk of heart attack, stroke, or cancer, especially breast cancer.
- Provide better-controlled safety data for women who have used Intrinsa for longer than six months.
- Collect more data on blood clotting differences with Intrinsa.

From the beginning of the advisory committee meeting, panelists questioned the lack of long-term safety data and worried about the potential for cardiovascular risk and cancer. Panel member comments included:

- "The FDA concludes with the applicant, P&G, that they have shown statistically significant differences associated with the treatment of patients in the primary efficacy endpoint of number of sexual events. However, we have questions about whether the significant change was produced by TTS and (whether) the proportion of women who experienced the improvement relative to placebo is clinically meaningful. Also, we have to look at safety data and evaluate the safety data based on its accuracy."
- "I think if there is one single element of safety that deserves the most scrutiny, it is the potential role of this patch in promoting blood clotting."
- "We have at least four to five pieces of data to suggest there is a high probability of excess CV (cardiovascular) disease, including evidence that androgenic testosterone levels are associated with coronary disease…This is a much too small safety database.

- "In light of the potential for off-label use of this product, we must have information from pre-menopausal, menopausal women, estrogen takers, and estrogen+ progesterone takers."
- "I'm concerned about breast cancer. We'd prefer not to have any surprises like we did with WHI (Women's Health Initiative, which enrolled nearly 17,000 women before it started detecting safety problems with hormonal therapy)."
- "The potential for this agent to increase the risk of cardiovascular morbidity and mortality is substantial, and (it) can only be marketed with post-marketing surveillance. I'm not devaluing symptoms and treatment, but I also don't want to expose seven million women to the risk of heart attack and stroke, and an increase of one sexual event per month is not an acceptable tradeoff."

THE P&G PERSPECTIVE

P&G officials insisted that Intrinsa is safe and effective and would be an important therapy to women with decreased sexual desire, decreased sexual activity, and increased distress. A P&G speaker said, "(These issues) affect all aspects of a woman's life, including her health, well-being, and relationship with her partner." P&G's director of clinical development said, "(Intrinsa) increased not just primary and secondary sexual function endpoints, but every sexual functional endpoint that we measured." P&G said any risks associated with a 300 µg/day transdermal dose are low and acceptable to patients based on a low level of withdrawals due to adverse events.

P&G developed three tools in order to gauge the endpoints of sexual desire, activity, and distress:

- **Sexual Activity Log (SAL)** – a weekly diary measuring sexual activity.
- **Profile of Female Sexual Function** – 30-day recall measuring domains of sexual function.
- **Personal Distress Scale (PDS)** – 30-day recall inventory measuring seven sexual function domains and distress associated with low sexual desire: desire, arousal, pleasure, orgasm, responsiveness, self-image, and concerns. Scores ranged from 0 to 100.

There were 12-month Phase III efficacy and safety studies, involving 562 (SM1) and 532 women (SM2), respectively. The primary endpoint was frequency of satisfying sexual activity, and the two key secondary endpoints were sexual desire and distress. P&G said that all three endpoints showed statistically significant improvement in women who received the patch compared to placebo. P&G also reported that improvements were seen in all other efficacy endpoints. Benefits were seen as early as four weeks and were maintained for the remainder of the 24-week efficacy period.

Phase III Intrinsa Trials

Study	Intrinsa (µg/day)	Number of patients	Baseline mean	Mean change from baseline at Week 24	p-value
Primary endpoint: Frequency of Total Satisfying Episodes					
SM1	0	273	2.94	.98	.0003
	300	276	2.84	2.13	.0003
SM2	0	255	3.19	0.73	.0010
	300	258	3.04	1.56	.0010
Secondary endpoint #1: Sexual Desire					
SM1	0	269	20.82	6.90	0.0006
	300	269	19.79	11.85	0.0006
SM2	0	257	23.37	6.21	0.0006
	300	252	21.67	11.38	0.0006
Secondary endpoint #2: Personal Distress					
SM1	0	266	62.57	-16.31	0.0006
	300	268	64.78	-23.55	0.0006
SM2	0	258	66.38	-18.27	.0091
	300	254	66.61	-24.34	.0091

In a clinical relevance study of 132 women from the Phase III trials, P&G said that 52% of women on Intrinsa said they had experienced a meaningful benefit from the patch compared to 31% on placebo.

Intrinsa Phase III Trials:
Patients classified as receiving clinically meaningful benefit (by responder analysis)

Study	Placebo	Intrinsa	p-value
Change from baseline in total satisfying episodes			
SM1	34.8%	45.7%	.0102
SM2	25.1%	42.2%	<.0001
Change from baseline in sexual desire			
SM1	34.6%	51.3%	<.0001
SM2	33.9%	49.2%	.0005
Change from baseline in personal distress			
SM1	39.1%	50%	.0117
SM2	39.1%	51.6%	.0056

Intrinsa Clinical Relevance Study

Patient Group	Interest in Continuing Treatment				
	Definitely not interested	Probably not interested	May/may not be interested	Probably interested	Definitely interested
Among patients reporting meaningful benefit	<5%	<10%	<10%	28%	55%
Among patients reporting ***no*** meaningful benefit	73%	20%	<10%	2%	<5%

P&G said that overall adverse events and withdrawals due to adverse events were generally similar for Intrinsa and placebo. A speaker presenter said, "Androgenic effects are infrequent, generally mild, and rarely led to withdrawal. There were no changes in lab values except a small change in red cell mass. Weight gain averaged about half a pound…The patch was very well-tolerated. No serious safety concerns have been identified to date." An endocrinologist and clinical investigator speaking on behalf of P&G said, "There was no evidence of testosterone accumulation over twelve months…There is no evidence of safety concerns with increased testosterone."

P&G officials identified several potential safety concerns, but they insisted that Intrinsa is safe. A speaker said, "We currently have 80 people in Year 3 of the extension, and one year from now we will have an additional 2,500 patient-years of exposure." As for unanswered safety questions, a P&G official said, "It is not uncommon to have unanswered safety questions at approval. It is important to keep in mind that we have seen no significant safety signals, and there is experience in the world of concomitant estrogen. Testosterone is not a new drug. Androgens and estrogens have been used for years in women. And we have proposed a rigorous independent post-marketing safety study." Among the potential safety concerns mentioned by P&G were: Androgenic skin changes, weight, blood pressure, liver dysfunction, polycythemia, cardiovascular disease, breast cancer, and other adverse events noted on male product labels.

Most Common Adverse Events in Intrinsa Phase III Trials

Adverse event	Placebo n=545	Intrinsa n=549
Upper respiratory tract infection	8.4%	9.1%
Headaches	6.4%	7.8%
Hirsutism	5.9%	7.3%
Acne	5.1%	6.7%
Alopecia	2.9%	4.2%
Anxiety symptoms	2.4%	2.7%
Voice deepening	2.2%	2.7%
Migraine headaches	1.5%	2.7%
Gastrointestinal and abdominal pains (excluding oral and throat)	0.7%	2.6%
Nausea and vomiting symptoms	1.5%	2.2%
Influenza like illness	1.5%	2.2%
Gastroenteritis viral	1.7%	2.0%
Weight increased	1.5%	2%
Disturbances in initiating and maintaining sleep	1.5%	2%
Hypertension	1.5%	2%

P&G said the percentages of patients reporting androgenic adverse events during the double-blind period was similar between treatment groups in SM1 and increased in the testosterone group compared to placebo in SM2. Most patients (78%) reporting an androgenic adverse event reported only one type of event.

Phase III Adverse Events *(24-week double-blind period)*

Adverse event	SM1		SM2	
	Placebo n=279	Intrinsa n=283	Placebo n=266	Intrinsa n=266
Any adverse event	79.6%	77.7%	74.1%	74.4%
Serious adverse event	2.5%	2.5%	2.3%	1.9%
Most common adverse events				
Application site reaction	39.1%	31.1%	28.9%	29.7%
Upper respiratory tract infection	9.3%	9.9%	7.5%	8.3%
Headache	7.5%	9.9%	5.3%	1.9%

Patients Reporting Androgenic Adverse Events *(24-week double-blind period)*

Adverse event	SM1		SM2	
	Placebo n=279	Intrinsa n=283	Placebo n=266	Intrinsa n=266
Acne	6.1%	6%	4.1%	7.5%
Alopecia	3.2%	3.2%	2.6%	5.3%
Hirsutism	6.5%	5.7%	5.4%	9%
Voice deepening	2.9%	2.5%	1.5%	3%
Severity of androgenic events as a proportion of events				
Mild	96.2%	98%	97.5%	91.5%
Moderate	3.8%	2%	2.5%	7%
Severe	0	0	0	1.4%

The severe androgenic event was a woman on the patch who experienced hoarseness that was probably related to the drug, according to P&G. One patient reported signs of clitoromegaly and was taken off the patch. There was no difference between Intrinsa and placebo when it came to facial hair in SM1, but there was a mild increase in primarily chin hair growth in SM2 among patients on the patch.

Two patients in the Intrinsa group reported serious adverse events assessed as possibly related to treatment: one patient had a transient ischemic attack and the other reported an episode of tightness in the chest, diarrhea, flushing, increased heart rate, nausea, tingling in the roof of the mouth, and diaphoresis. The adverse events were resolved while the patient was on the drug. One patient on placebo died during SM2 due to a basal ganglia hemorrhage.

Four women in the program were diagnosed with breast cancer. One case was a placebo patient in a Phase II study. The others were:

- 63-year-old diagnosed with invasive breast cancer after five weeks on Intrinsa.
- 56-year-old diagnosed with tubulobar carcinoma after 37 weeks on Intrinsa.
- 50-year-old diagnosed with DCIS after 24 weeks of Intrinsa.

A P&G menopause specialist told the panel that Intrinsa could help many women. She said, "No testosterone product currently is available for treating surgically menopausal patients with HSDD…Unfortunately, we're using products that have been formulated for men and putting women at risk for high doses of testosterone…In 2003, about 21% of total prescriptions for branded male testosterone products were actually written for women. In the same time period, more than one million prescriptions were written for compounded or generic testosterone products for women…Some of you may have questions about clinical meaningfulness. The increase in satisfying sexual events may not seem like much, but this increase represents an important change to these women."

Measurement	Baseline	Change from baseline
Satisfying sexual activity (4-week period)	2.9	+1.8
Desire	20.7 (points)	+10.8
Distress	65.7	-22.7

P&G told the panel that it wants to do a Phase IV observational study on safety. The company's director of pharmacovigilance and epidemiology said, "There were no serious safety signals that merit follow-up. Nevertheless, we plan to monitor women for longer periods of time…The issues raised by the FDA include the inability to capture medical claims data on women over 65. P&G's response is that women over 65 represent 2%-3% of potential Intrinsa users." The proposed 5-year study would compare event rates in Intrinsa users to non-users. The endpoints would be cardiovascular disease (CHD, stroke) and cancer." P&G said that it would get input from outside experts, and an independent safety review board would report to the FDA.

P&G has ongoing trials of surgically menopausal women with 321 subjects in Year 2 of a 3-year extension. There are two placebo-controlled studies in naturally menopausal women on estrogen+progesterone (E+P). They are 6- and 12-month trials with 400 patients in each. P&G also has a study of TTS without estrogen or E+P with projected enrollment of 750 in three arms.

THE FDA PERSPECTIVE

An invited expert gave a presentation on the patch's side effects and potential risks. He concluded, "With more women being treated for longer periods of time, what are the long-term effects of androgenic signs and symptoms and what is the risk on breast and uterine tissue?" He said that concerns about testosterone administered to women include:

- **Androgenic effects**, including acne, hirsutism, and virilization. An expert said, "Testosterone can act directly on muscle, bone, virilization, brain, and sexual function. Acne, hirsutism, and virilization are common effects of testosterone. Clinical presentation is usually acne, including hair growth, clitoromegaly, balding, voice deepening – all commonly associated with high doses of testosterone…In general, it is dose- and duration-dependent, and most of these effects are reversible. It is unclear whether balding is fully reversible, and clitoromegaly may take years to see any resolution."

- **Cardiovascular effects/risk.** The data on the effect of testosterone on women is mixed. A speaker said, "It's hard to say what the long term effect will be; it doesn't seem to be accumulation of testosterone in the skin, but the issue of dosing is extremely important and (so is) monitoring of doses…When testosterone is going to be used in larger numbers of women, the question is when will testosterone get to levels beyond the normal range? There is very little two-year data that's out there."

- **Lipids, vascular, glucose tolerance, hemotopoietic, insulin, fibrinogen.** A physician said, "Testosterone has a minimal effect on vascular reactivity, and perhaps it could be beneficial." However, he said that plasma viscosity "is of great concern; we know that increased plasma viscosity is an established risk factor for cardiovascular disease and predicts cancer development." He also said that testosterone is involved in stimulating production of erythropoietin, and, in men, it's clear that testosterone can cause erythrocytosis. "Glucose metabolism is clearly a risk factor for cardiovascular disease both for hypoglycemia and hyperinsulinism. The challenge ahead is to determine what is the relationship of testosterone metabolic syndrome, polycystic ovarian syndrome (PCO), and how to put that into context. Is it testosterone per se that is cardiovascular or metabolic to estradiol?"

- **Endometrial and breast effects (and uterine tissue).** This expert said, "There seems to be a relationship between (androgenic) hormones and the development of disease…Women with increasing doses of androgenic hormones will have an increased risk of developing endometrial cancer…When testosterone gets to the male level, it will be aromatized to estrogen and runs the risk of unopposed estrogen in the endometrium. With low doses there have been no cancers reported, but there has only been one study." A physician said, "There may be a relationship between high androgenic testosterone and breast cancer – hyperandrogenism associated with metastasis. There seems to be a relationship here. Due to the fact that there are androgen receptors found in 50%-90% of breast tumors, this testosterone may act directly to stimulate breast epithelium."

FDA medical officers also presented their analysis of P&G's efficacy and safety data. A key concern was the clinical relevance of the efficacy measurements. One medical officer, presenting the efficacy data, said that Intrinsa use resulted in a relatively small increase in satisfactory sexual events. He said, "We agree the endpoint changes were statistically significant compared to the placebo effect, but the key issue for us is really the clinically significance of the findings." He added, "Although there is a clear treatment effect for both

placebo and TTS in the two Phase III trials, we can easily see the testosterone effect did not return women to the values of a normal woman as determined by the applicant." The reviewer said that 52% of women using Intrinsa said they experienced meaningful benefit from the patches compared to 31% on placebo.

As far as the endpoints are concerned, he said that "small mean changes were noted and there was strong placebo effect relative to TTS effect that persisted throughout the two six-month blinded trials…While significant statistically, the clinical significance of one event vs. placebo is not clear to the division."

Mean baseline score was 65 for all participants for secondary endpoints. The difference between placebo and treatment was 6-7 points for Intrinsa compared to placebo. An FDA staffer said, "We're not sure of the clinical significance of this change…The same concern is seen with the other secondary endpoint for sexual desire. The overall mean score was 21. Placebo increased an average 6-7 points while the testosterone (Intrinsa) group increased 11-12 points. The difference between testosterone and placebo is approximately 5 points in the first study and 5.2 in the second study; once again, the clinical significance is a small number change and is the issue…Although there is a clear treatment effect for both placebo and TTS in the two Phase III trials, we can easily see that the testosterone effect did not return to the values of a normal woman as determined by the applicant."

Study of Normal Women with Normal Sexual Desire and Intrinsa Trial Participants

Measurement	Normal women	Study Participants in Phase III	
		Baseline	Intrinsa
Baseline sexual events per 4 weeks	12	3	5
Desire (on 0-100 scale)	65	21	33
Distress (on 0 to 100 scale)	5	65	41

The FDA reviewer said, "These were minimal changes, and the difference between placebo and TTS ranged from 12%-14% in responders in the Phase III studies combined…There was a small statistically significant increase in mean numbers of SSEs and small changes in secondary endpoints…These changes in the testosterone treatment do not approach the normal values seen in hormonally matched women as determined by P&G."

FDA officials also had concerns about the safety of Intrinsa, including the risks of long-term testosterone combined with estrogen. The safety issues that were highlighted included:

- **Androgenic effect.** "Overall, androgenic events showed increasingly frequently in women on TTS, including androgenic adverse events overall…There appears to be an association between higher levels of free testosterone and higher levels of hirsutism and acne."
- **Cardiac risk.** "We are concerned about the potential impact of TTS on a number of cardiac risk factors, and several appear to be linked. Metabolic syndrome is an independent risk factor for CV risk. Components generally included glucose intolerance, hypertension, dyslipidemia. Metabolic syndrome is twice as prevalent in African-American women than Caucasian women."
- **Lipids.** "While, on average, lipid value showed little mean change, some parameters were of concern."
- **Glucose.** "The change from baseline for glucose levels appears to increase with TTS exposure."
- **Insulin.** "Although the changes in the markers are small, these small trends may be magnified in the total target population."
- **Blood pressure.** "The effect of TTS on blood pressure was also of interest…Here you can see a rise occurs in 5% more subjects who received TTS for 6-12 months compared to placebo. Similarly, 4% more subjects had rises of diastolic blood pressure in TTS compared to placebo."

The FDA cited several limitations to the current Intrinsa data, including:

- The placebo-controlled phase was only six months.
- Long-term use was limited to 12 months for 494 patients and 18 months for 127 patients.
- Women with diabetes and cardiac disease were not studied.
- Limited data was available on naturally menopausal women.

The FDA staff also had concerns about P&G's proposed post-marketing pharmacovigilance plan, including:

- Does a claims-based cohort study provide the same level of (safety) evidence as a randomized, placebo-controlled trial?
- Projected sample size is inadequate.
- The study is powered, but may miss important but lower risks. They suggested a sample size of almost 17,000 is needed to achieve adequate detection.
- No information is included on the power to detect a breast cancer risk.
- Long latency may not be detected. In the Women's Health Initiative estrogen+progesterone study, breast cancer rates did not diverge until Year 4.
- There could be a high turnover in plan coverage.

The FDA presenter said, "The WHI (Women's Health Initiative) had far-reaching effects. We learned that data was discrepant. Lessons learned indicate the need for heightened scrutiny of hormone therapy in post-menopausal women… The sample size and duration of treatment is inadequate to

exclude serious risks including cardiovascular disease and breast cancer. The population studied is inadequate to identify important risks in naturally menopausal women using E+P and subgroups at higher risk for CV morbidity."

COMMENTS BY PUBLIC WITNESSES

The public testimony was generally unfavorable towards Intrinsa.

Con:

- "It's a no-brainer…Intrinsa is unsafe and will cause a deluge of litigation filed by women injured by the drug. It should be banned…Intrinsa is the most hazardous non-narcotic drug ever presented for FDA approval." – *Dr. Mark Klein*
- "I see today as a perilous moment in the history of women …The Intrinsa trials are grossly inadequate to assess the risks of extended testosterone treatment… Intrinsa is not a glass of chardonnay." – *Dr. Leonore Tiefer, New York University Professor of Psychiatry*
- "There are many questions to resolve including dosage issues, duration of long-term effects and potential adverse reactions." – *Karen Hicks, PhD, a sexual health educator and founder of the Dalkon Shield Information Network*
- "The therapy was only briefly evaluated and not in populations of women who may be at increased risk. We are deeply concerned about the enormous potential of off-label use in inappropriate populations. In light of the skyrocketing increase of breast cancer, while much remains unknown about (Intrinsa)…All women at risk for breast cancer must proceed with extreme caution before pursuing hormonal treatments for other medical conditions…the long-term effects of hormonal therapies may not be known for many years. Approval will be one more incidence where women become guinea pigs." – *Ann Kasper, Breast Cancer Action*
- "Is an increase in sex from four to five times over a month worth the possibility of increased risk in breast cancer or coronary heart disease? Is the FDA actually considering approval of this product?" – *Dr. Sid Wolfe, Public Citizen*
- "This is a drug prematurely coming to closure on something where we don't understand the basic science." – *Kim Wallen, PhD, Emory University Professor of Psychology and Behavioral Neuroendocrinology*

Pro:

- "I have first-hand experience with the positive effects of Intrinsa and I would like to experience those feelings again." – *Intrinsa patient*
- "(Intrinsa is) efficacious and safe; these are statistically significant based on the information provided to the FDA. It is the opinion of AACE that the patch can achieve improved sexual function with minimal incidence of adverse effects." – *American Association of Clinical Endocrinologists*

THE ADVISORY PANEL DISCUSSION

Panel member and cardiologist Dr. Steven Nissen of the Cleveland Clinic said too few women were studied before P&G applied for approval. He said he thinks P&G needs to study at least 5,000 women for several years to see if the patch increases cardiovascular risk.

The panel dismissed P&G's proposed post-marketing study that would compare rates of cardiovascular disease and cancer in 5,500 women expected to use the patch in the first year against matching women from a database of 10 million patients. P&G told the panel that it will soon have more safety data for 200 women who have used the patch for one year, as well as safety data for 100 women who have used it for 18 months. Eighty women have used the patch for three years. This was clearly not enough data for the panel.

Although the director of FDA's Division of Reproductive and Urologic Drugs told the panel that 15 out of every 100 women using Intrinsa experienced a beneficial effect due to testosterone, and the panel (by a 14 to 3 vote) agreed that the benefit of Intrinsa compared with a placebo was "clinically meaningful," several panel members questioned the efficacy of the drug.

Panel members questioned P&G officials about safety and how they measured Intrinsa's efficacy. Questions included:

- What are the effects of high levels of testosterone?
- A panel member asked about study dropouts and their relationship to high doses.
- Would P&G's proposed long-term safety plan bring up privacy issues?
- Are there potential risks for breast cancer and cardiovascular disease in women with above average BMI?
- Another panel member asked about the significance of frequency of satisfying sexual encounters. The exchange was interesting:

Panel member: "If these people had a normal sexual relationship prior to their ovariectomies, why aren't they going back to their 'normal' state. If the answer is androgen replacement, why aren't they back to normal rather than one increased encounter a month?"

P&G: "We didn't ask what their normal level was."

Panel member: "Isn't it important to have that data – what you consider normal for that group of women? The androgen may not totally explain what's going on here…I'm not

disagreeing that the patients are better, but the question is why aren't they back to normal if the answer is androgen?"

P&G: "Four events in three weeks is quite a lot…The typical American experience has nothing to do with Sex and the City; if that means you're doing non-intercourse events, but it's a loving close intimate relationship, then there's nothing to treat – there is no normal sexual function. The most important thing is that it's working for the woman and that there's no associate distress…Couples in their 50s have between 1.5 and 2 sexual encounters per week or 7 to 8 per month…That is normal."

Panel member: "What is the effect of testosterone on breast tissue?"

P&G: "All studies show that testosterone is not raising the level of concern about breast cancer; in fact, it is possibly lessening concern."

Other interesting question-and-answer exchanges and panel comments included:

Panel member: "Was there any effort to eliminate women with evidence of metabolic syndrome? Or any other exclusion criteria applied?"

P&G: "Androgens have very little impact on glucose metabolism themselves."

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Panel member: "Why are African-Americans and Hispanic populations under-represented in this study?"

P&G: "It's notoriously difficult to recruit minorities. We tried to recruit as many as possible. Six percent is not representative of the U.S. population, but it's better than a lot of clinical trials I've been involved with."

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P&G: "In the younger age group, testosterone might be protective."

Panel member: "The phrase is **might be**. And for charged issues, I think we should be conservative and do a larger study."

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Panel member: "What about the risk of breast cancer? I was involved in a study that is very different from what I see here. Testosterone was related strongly to breast cancer risk in these women...This could translate into increased risk of breast cancer in this group as a whole – maybe 70%, possibly to the doubling of risk. Could you comment on that?"

Another panel member: "These data don't show that epidemiologic studies show strong association of testosterone levels with breast cancer risk in post-menopausal women."

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Panel member: "When they (patients) were asked (about) interest in continuing the treatment, if that was a meaningful experience for them, and if it made a difference – how am I to interpret that when I see 70% saying Definitely Not or 6% Definitely. Why weren't more people interested in continuing?"

Another Panel member: "What was the percentage of people on the patch who said they would definitely not or probably not use the patch?"

P&G: 49%

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Panel member: "What's to keep this from being called the female Viagra (Pfizer, sildenafil)?"

P&G: "It's not a female Viagra. This is more something that works centrally on desire; desire goes up and sexual activity goes up."

Panel member: "What part of the brain is that in?" (audience/panel laughter)

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Panel member: "It all hinges on…one question: Were women briefed as to what is meaningful benefit? We have to interpret scores as well as the responder analysis, and as I understand the results, we have a change of just about one event in four weeks."

P&G: "No – it's two events."

Panel member: "Taking away the placebo effect, the stress 6.7 and desire 5.1, and what we're left is the difference between treatment and placebo…and I think the instrumentation in this study was really well done...but our issue is interpreting those median group scores…The important thing for me is: Is it fair to say that the difference between TTS and placebo was one more event every four weeks? You win on that, but for the distress it was greater than 8, and we got a difference of 7, so we're just on the margin – is that fair to say?"

P&G: "No, clinical relevance is established through some operational paradigms. This particular paradigm used the anchoring technique, tied back to patient perceptions."

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Panel member: "I'm curious about how quickly the treatment got up to a clinically significant level of change. I wish we had more than one-year data. And I still feel it strongly needs to be used in chronic dosing."

P&G: "If you remove the patch the effect goes away."

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Panel member: "The idea of ignoring the placebo group and assuming activity in the placebo group is an indication of the placebo effect. I notice in the package insert that the only information given is baseline to follow-up in the testosterone group. I'd like some comment on why you would regard that placebo effect so strongly…The patient going to the doctor, trying to increase frequency of intercourse and after a while giving up, in the real world, the question is, would this have happened anyway?"

P&G: "What we found was every single aspect of HSDD improved in every way…We will never take hormone therapies lightly. We're sometimes undermining patients' abilities to weigh risks and benefits."

Panel member: "Wouldn't it be useful in the insert to point out what the placebo effect was?"

Questions for FDA staff were mainly about whether the benefits of TTS outweigh the risks.

Panel member: "There is a fractional number of satisfactory sexual events. Has there been thought of trying to look at these as combined endpoints? Why is satisfactory sexual events thought to be the primary endpoint in this area?"

FDA: "This is a new area for everybody. It doesn't have clean endpoints. We realize many investigators have questions about this being the primary endpoint."

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Panel member: "You're insinuating you weren't 100% 'with' the endpoint, and you've said that this is a new area: Quality of Life drug. But that's not true. You've looked at inhibitors with instruments similar to what we're using here. When reviewing the data from the newest PDE-5 inhibitors (e.g., Viagra) were those more robust than what we're seeing here in terms of quality of life changes?"

FDA: "We can look at this in many different ways…One way is that it requires us to expose 100 women to testosterone in order for 15 of them to have a borderline clinically meaningful effect attributable to testosterone, and that's basically what it boils down to. That's not saying there isn't clinically meaningful effect for some women. But in a population setting is that benefit worth the risk?…We have to weigh those things and make some kind of decision."

FDA Questions for the Advisory Committee – and the Panel Votes

Question 1: Do the efficacy data represent a clinically meaningful benefit above that of placebo for surgically menopausal women with HSDD who are taking concomitant estrogen? **YES by a vote of 13 to 3, with some voting yes reluctantly.**

Question 2: Is patient exposure adequate to demonstrate long-term safety? **UNANIMOUSLY NO**

A panel member commented, "What we know is exactly what was done in the trials. This is the database that we have, and we're asking whether we have an adequate safety base. That couldn't be more clear, and I don't think we have to dance around it. We have at least four to five pieces of data to suggest there is a high probability of excess cardiovascular disease, including evidence that endogenous test levels are associated with coronary disease. Outliers are much more likely to have elevated lipids, sugars, worse insulin resistance, blood pressure (increases) sometimes in the range of 10-19 mmHg, which is highly associated with cardiovascular risk. We also have data on the known risks of estrogen and progesterone in the WHI study. So, given that, my estimation is that it is at least in an order of magnitude too small for us to assess a fair use. I think this is much too small a safety database."

Question 3a: Are there safety concerns or unanswered questions that need to be studied? **UNANIMOUSLY YES**

What are the concerns/unanswered questions? Panel members explained:

- "I'm worried about pre-menopausal women and fetuses. Yes, there are safety concerns, and, yes, they need to be studied. Also breast cancer, and the evidence in my mind is inconsistent toward an association. My bias is that the androgens are protective, to be honest, but follow-up is needed in a broad well-done post-approval study looking specifically at the incidence of breast cancer."
- "I want to see more African-American women studied."
- "Even though there may be some increased risk with testosterone, I don't think patients would do any different analysis than if they came in for hot flashes, so patients will make that same risk benefit analysis…I agree we don't have enough information from a long-term study."

Question 3b: Should these concerns or questions be studied prior to approval of the product? **UNANIMOUSLY YES**

- "I think this drug will require more study…I was hopeful that we would have a product, that we'd get patients where we know the risk and benefits, and this product does allow that potential, but at a minimum, we need to look at it in the naturally menopausal patient."
- "There's going to be tremendous interest in this product; I don't see how this can go to market without the data that the company looks like it's almost finished with on naturally menopausal women because they'll be taking it as well. I think it's good to wait a little bit."
- "We need adequate long-term data that demonstrate efficacy and safety – and we need an adequately powered study."

Question 3c: If yes, what studies do you recommend?

- "In menopausal women, the leading cause of death is cardiovascular disease. It represents a huge burden of morbidity. I believe you need a prospective, adequately-sized, long-term study. I'd do it in aspirin-eligible women...and it's not going to be 500 or 1,000 patients, it's going to be 5,000 or 10,000 patients. The risk that was seen with Vioxx (Merck, rofecoxib) was very modest, but when you translate that to 20 million Americans…"

Question 4: Are the efficacy and safety data adequate to support approval of Intrinsa? **UNANIMOUSLY NO** ♦