Statement to the Food and Drug Administration
Advisory Committee for Reproductive Health Drugs
on the Testosterone Transdermal System (Intrinsa)

by Amy Allina, Program Director
National Women's Health Network
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I am speaking on behalf of the National Women's Health Network (NWHN), a nonprofit organization that works to improve the health of all women by influencing health policy and supporting consumer decision-making. The Network accepts no financial support from pharmaceutical companies or medical device manufacturers and has no financial stake in Intrinsa or its potential competitors.

Procter &Gamble (P&G) has conducted research that shows their testosterone patch may offer some help to women who have had their ovaries removed, are taking estrogen and are experiencing a low level of sexual desire that is a problem for them. There are limitations to the data in this application that concern us, particularly the small number of women studied and the lack of information about long-term safety and effectiveness. But putting those limitations aside for a moment, it does appear that Intrinsa could offer some benefit to the narrow group of women in whom it has been studied. The need in that group is real, and the chance to provide real help to women with the problem of low sex desire is hard to pass up.

As women's health advocates, however, we cannot consider this product in a vacuum, and neither should FDA. The world changed when the Women's Health Initiative (WHI) revealed the negative long-term health effects of hormone therapy. A six-month study of a testosterone patch that would be the first drug of its kind may have seemed adequate before, but it's not today.

Long-term safety
Women who might stand to get a benefit from the testosterone patch need to know about its long-term effects on their health. The limited knowledge we have about testosterone raises concerns about both breast cancer and heart disease. In the wake of the WHI, it's appropriate and necessary to exercise special caution about the safety of long-term hormone use without long-term data.

Research shows that high testosterone levels predict a greater likelihood of breast cancer recurrence in women who have had it.[i] But the patch has not been studied for an adequate period of time to find out whether it might increase risk of breast cancer in women who have never had it. The only early indication that might have been available from the company's data would have

been in the mammographic study, but FDA noted in its medical review there are several limitations to that study which make it difficult to determine what effect the testosterone patch might be having on breast tissue. In addition to the short duration of the study, the use of a comparison group of women taking combined estrogen/progestin therapy may obscure the effect of the testosterone since estrogen/progestin therapy has, itself, been shown to increase both breast density and risk of developing breast cancer.

The short-term data that P&G has collected so far are also not able to provide any reassurance about the effect of their product on risk for heart disease. In fact, there are hints even in the limited data available that may be cause for concern. As FDA noted in its medical review, "events occurring uniquely in the extension phase [...] are concerning in aggregate, as they include palpitations, chest pain, fatigue, increased heart rate, dizziness, dyspnea and hypertension, all of which could reflect cardiovascular events." Although there is no placebo comparison for the extension phase, the average age of women in the combined trials was 49, so these problems cannot simply be dismissed as expected background in elderly women. Followed over a longer period of time, as women in the WHI were, such events might turn out to be warnings of future more serious cardiovascular harm. The fact that lipid profiles were similar in the testosterone and placebo groups is not adequate reassurance since lipid levels failed to predict the cardiovascular problems that were eventually found to be associated with hormone therapy in the WHI.

Balance potential to help with potential to harm

In addition to a rigorous assessment of whether the data presented on safety and effectiveness of this product are adequate to support approval of the application, FDA must balance the benefit that the testosterone patch may offer to a small group of women with the health risks it may pose to many more. It would be naive and irresponsible to pretend that this drug will only be promoted and prescribed to women who are exactly like those in the trials.

- Even a cursory scan of health websites and books dealing with sexual health issues shows that a much broader group of women are already being advised to use testosterone for the problems they are facing in their sex lives.[ii] This advice is not directed solely to women who have had their ovaries removed; it's not even limited to menopausal women. Women who are still in their reproductive years are being advised by doctors and medical experts that testosterone can solve their problems with sex. Use by women in this age group raises a whole new set of questions about the safety of this drug to which we have no reliable answers. For example, we know that testosterone use during pregnancy is contraindicated, but how might it affect future fertility?

- Testosterone is being promoted to women for other unproven purposes as well including anti-aging, decreased stress, increased energy, muscle building and mental sharpness. It is also recommended to supplement oral contraceptive pill use for women who experience a decrease in sex drive as a result of taking the Pill.[iii]

Although real world use rarely, if ever, mimics clinical trial design precisely, in this case it's very possible that the vast majority of testosterone patch use will be by women who are different from the trial population in important ways that pose serious health risks.

Concerns about the proposed product label and patient information leaflet

- The text for the proposed patient information leaflet for the testosterone patch says that women who have or have had breast cancer should not use. The contraindications listed on the proposed product label, however, only state that the patch should not be used by women who have breast cancer, without mentioning those with a history.

- The first paragraph describing Intrinsa in the proposed patient information leaflet says that "Intrinsa is for the treatment of low sexual desire causing distress or concern." It makes no mention of the fact that this product is only intended for use by women who have had their ovaries removed and are taking estrogen therapy. That information doesn't appear until the third section of the leaflet.

Conclusion

Clearly what we don't know about this drug, even for those women in whom it has been tested, is significant. And the unknowns for women who are not surgically menopausal are immense. Taken together with the certainty that once approved the testosterone patch will be prescribed for unapproved applications that have not yet been studied, these unanswered questions must weigh heavily in FDA's decision. The NWHN urges the agency to postpone a decision on the application until further data about use by broader populations of women are available.

References

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iii. Testosterone Replacement for Women, http://www.usdoctor.com