Testosterone Transdermal Patch (Intrinsa®) for Female Hypoactive Sexual Desire Disorder (HSDD)

REVIEWED POSITION STATEMENT

Since the launch of Intrinsa in 2007 no formal applications for inclusion of Intrinsa on the local Trust formulary have been received. Worcestershire Area Prescribing Committee has undertaken an appraisal of the literature in order to provide a recommendation for use. This position statement is an update to the last version issued in April 2009.

**Recommendation:** Intrinsa is not recommended for use within Worcestershire.

Female Hypoactive Sexual Desire Disorder (HSDD)
- HSDD has been defined as the persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for or receptivity to sexual activity, which causes personal distress or interpersonal difficulty. However there is debate whether lack of sexual desire is a disorder. What is more accepted is that the lack of desire that causes distress to the woman or problems in the relationship with her partner is clinically important.
- Testosterone production is reduced in post menopausal women. Testosterone deficiency is thought to contribute to female sexual dysfunction but low levels of testosterone can not be used to predict the presence or severity of HSDD in women.
- Intrinsa® (testosterone transdermal patch, TTP) has a specific license for the treatment of hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised (surgically induced menopause) women receiving concomitant estrogen therapy up to 60 years of age; Diagnosis of HSDD requires a full psychological and medical assessment by a specialist.

Clinical Efficacy
- Efficacy was not demonstrated in clinical trials for women taking oral conjugated equine oestrogens or women over 60 years of age. Diabetics were excluded from the trials.
- 4 double-blind, randomised, controlled trials showed a large placebo response with up to 46% of TTP patients and up to 35% of placebo patients classed as responders for the primary end point.1-4 54% of patients on TTP were non-responders.5
- The primary outcome measure in the studies was the change in the number of satisfying sexual episodes during the last 4 weeks of treatment compared with baseline. In 2 studies, the sexual desire domain of the Profile of Female Sexual Function (PFSF) was also used as a primary endpoint.3,4 Both outcome measures were assessed using tools developed by the manufacturer with no external validation, this together with the small improvements means the clinical relevance is questionable.
- Results from 3 studies showed that the increase in number of satisfying sexual episodes was significantly greater for TTP patients than placebo patients (average increase of 2 episodes per 4-week period compared with 1 episode, from a baseline of 2-4 episodes in 4 weeks). There was no significant difference compared with placebo in the fourth study (which may have been underpowered).4
- In all 4 studies, there was a significantly greater improvement for the sexual-desire domain of the PFSF compared with placebo after 24 weeks treatment (increases of 6 or 7 points more than placebo on a 100-point scale). The differences for women using 150microgrammes and 450microgram patches were not statistically significant compared with placebo.5 Significantly greater improvements after 24 weeks treatment were reported for TTP women compared with placebo in the remaining 6 domains of the PFSF in 2 studies1,2 in 5 domains in 1 study4, and in 1 domain (sexual arousal) in the final study.3
- There is no new evidence regarding efficacy since the previous review (April 2009)

Adverse Effects
- The main studies of efficacy above did not evaluate use beyond 24 weeks.
- More patients in the TTP group withdrew from the trials compared to the placebo group, mainly because of hirsutism and weight gain. Other reported adverse effects include voice deepening, acne and alopecia. There is insufficient data to assess whether the acne, hirsutism and voice deepening are reversible on discontinuation.

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Safety and tolerability have been further evaluated in a follow-up trial from 2 of the previously reported trials. This open-label extension followed patients up for up to 4 years.

- 967 patients received at least 1 application of testosterone; mean exposure rate of daily TTP throughout the study period was 13.6 months per patient.
- 46% discontinued treatment during the study (most commonly due to voluntary withdrawal 19% and adverse events 15%) and 46% declined to continue treatment at the next annual extension.
- The majority of adverse events (total 73% year 1, 48-56% years 2 to 4) were androgenic or application site and were mild. 4.7% serious adverse events occurred during the study period; 3 were assessed as possibly related to treatment. No patients died during the 4 year active treatment period. Few cardiovascular events were reported, the majority were palpitations (12). 2 cases of angina were reported and no myocardial infarctions occurred during the 4 years.
- A total of 7 patients were reported with forms of breast cancer (3 invasive and 4 ductal in situ); these arose at different stages of treatment including one year after discontinuation. The study size and duration is insufficient to identify changes in cancer growth rates and diagnosis.
- This trial has major limitations in set-up and design with high withdrawal and drop-out rates resulting in very few patients being assessed over the longer term period – with just 4.5% and 43 patients completing 4 years of treatment and assessment. The outcome of this trial has not been used to change the SPC for Intrinsa, which states that “efficacy and safety of Intrinsa have not been evaluated in studies of longer duration than 1 year; it is recommended that an appraisal of the treatment is undertaken every 6 months”.

Testosterone patches have not been compared with implants or any other current treatments

There remains a need for further placebo controlled trials to assess the long term safety issues especially with regard to potential harmful effects on breast tissue and the cardiovascular system.

An interim analysis of a drug utilisation review suggests that there is significant use of the product outside of the product license (>70%). This means that the safety profile is limited for this group of patients as they would have been excluded from participation within the trials reported.

### National Guidance

The following guidance on the use of testosterone patch (Intrinsa®) for the treatment of female hypoactive sexual desire disorder is available:

**MTRAC (October 2007):** ‘The testosterone patch is not considered suitable for prescribing. Current clinical evidence for efficacy is weak, based on short-term (24-week) trials using subjective outcomes. The size of benefit found was small, with questionable clinical relevance and a large placebo effect. There is concern about potential harmful effects of long-term use on breast tissue and the cardiovascular system (and endometrium if used outside the product license.)’

**Scottish Medicines Consortium (August 2007):** ‘not recommended for use within NHS Scotland for the treatment of hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised (surgically induced menopause) women receiving concomitant oestrogen therapy. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.’ SMC looked at trials Ref: 1 & 2.

As with any policy recommendation, the PCT will always consider exceptional cases according to individual need.

### References: