Hormone Replacement Therapy with Implantable Hormone Pellets

AHM

Clinical Indications

- **Estrogen**
  - Implantable estradiol pellets is considered experimental and investigational because they have been shown to produce unpredictable and fluctuating serum concentrations of estrogen

- **Testosterone**
  - Implantable testosterone pellets (Testopel pellets) is considered medically necessary for 1 or more of the following indications
    - As second-line testosterone replacement therapy in males with congenital or acquired endogenous androgen absence or deficiency associated with primary or secondary hypogonadism when neither oral nor intra-muscular testosterone replacement therapy is effective or appropriate
    - For treatment of delayed male puberty

- Implantable testosterone pellets is considered experimental and investigational for the treatment of symptoms associated with menopause as this use remains unlaeled and unsubstantiated. Implantable testosterone pellets are considered experimental and investigational for all other indications

Evidence Summary

- **Background**
  - While implantable estradiol pellets have been suggested as treatment for symptoms of menopause, there are no United States Food and Drug Administration (FDA)-approved, commercially available formulations of implantable estradiol pellets available in the United States. These formulations of estradiol have been shown to produce unpredictable and fluctuating serum concentrations of estrogen. The FDA's Fertility and Maternal Health Drugs Advisory Committee unanimously agreed to terminate compassionate investigative new drug (IND) programs for estrogen pellets as a last-resort treatment of menopausal disorder. The Committee noted the risk of bleeding and infection, the lack of information on release rates, difficulty in reversibility of the drug, increased feasibility of over-dosage of the drug, and increased risk of non-compliance with safety measures [such as] the addition of progestin.

- Implantable testosterone pellets may be indicated as second-line testosterone replacement therapy for males. Testosterone implants (Testopel Pellets) are commercially available in the United States. Androgens are primarily indicated in males as replacement therapy when congenital or acquired endogenous androgen absence or deficiency is associated with primary or secondary hypogonadism. Primary hypogonadism includes conditions such as: testicular failure due to cryptorchidism, bilateral torsion, orchitis, or vanishing testis syndrome; inborn errors in testosterone biosynthesis; or bilateral orchidectomy. Hypogonadotropic
hypogonadism (secondary hypogonadism conditions include gonadotropin-releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury as a result of surgery, tumors, trauma, or radiation, and are the most common forms of hypogonadism seen in older adults.

- If testosterone implants are to be used for treatment of androgen deficiency due to primary or secondary hypogonadism, the usual adult dosage is 150 to 450 mg subcutaneously every 3 to 4 months, or, in some cases, as long as 6 months. Dosage adjustment is needed to accommodate individual clinical requirements for such life changes as induction of puberty, development of secondary sexual characteristics, impotence due to testicular failure, or infertility due to oligospermia.

- For treatment of delayed male puberty, a 6-month-or-shorter course of androgen is indicated for induction of puberty in patients with familial delayed puberty, a condition characterized by spontaneous, nonpathologic, late-onset puberty, if the patient does not respond to psychological treatment. If subcutaneous testosterone implants are to be used, the usual dosage is to be determined by the physician. Low doses are used initially and increased gradually as puberty progresses.

- Filho et al (2007) retrospectively reviewed the medical records of 258 post-menopausal patients using estradiol and testosterone implants as combined hormone therapy to evaluate the effects of testosterone on the endometrium after 2 years of continuous use. Endometrial thickness was measured by ultrasonography. Histology was performed on samples of thickened endometria obtained during hysteroscopy with biopsy. In the 44 patients in whom endometrial thickening was greater than 5 mm at the end of the second year of implant use, the most frequent finding at hysteroscopy was polypoid lesion in 61.3 % of cases, followed by normal uterine cavity in 31.8 % of cases and submucous myoma in 6.8 %. Histology of the endometrial samples confirmed endometrial polyp in 38.6 % of cases, a histologically normal endometrium in 31.8 % of cases, simple endometrial hyperplasia in 20.4 % of cases, and myoma and atrophic endometrium in 4.5 %. It is possible that testosterone may exert its anti-proliferative effects on the endometrium but not on polyps in an action similar to that exerted by combined estrogen/progestin therapies. A greater incidence of simple, low-grade endometrial hyperplasia was found in this study compared with studies using continuous estrogen/progestin regimens. The use of progestins as the ideal endometrial protection should therefore be re-considered.

- Fennell and colleagues (2010) compared the 2 long-acting depot testosterone (T) products -- subdermal T implants (TI) and injectable T undecanoate (TU) -- for maintenance of testosterone replacement therapy (TRT). Men with organic androgen deficiency (n = 38) undergoing regular TRT were recruited for a 2-period, randomized sequence, cross-over clinical trial without intervening wash-out period of TRT maintenance. For both depot T products, their pharmacokinetics and pharmacodynamics were evaluated using a range of androgen sensitive clinical, laboratory and quality of life measures as well as preference for ongoing treatment after experience of both products. The 2 depot T products had distinct pharmacokinetics and were not bioequivalent. However, there were no consistent clinical differences in a comprehensive range of pharmacodynamic measures reflecting androgen effects on biochemistry and hematology, muscle mass and strength, and quality of life, mood and sexual function. The majority (91 %) of participants chose TU over TI at study completion. The authors concluded that despite significant pharmacokinetic differences, the 2 depot T
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products are clinically interchangeable allowing for choice dependent on patient and physician delivery preference in practice; but most patients preferred the injectable over the implantable form.

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