Review and Evaluation of Pharmacology/Toxicology Data

HFD-580/Alex Jordan, PhD

NDA 20-908

Sponsor: Novo Nordisk Pharmaceuticals.

Submission: May 28, 1998

Vagifem (17B-estradiol) 25 ug vaginal tablets

Indication: To treat the symptoms of atrophic vaginitis.

/S/ 10/21/98

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Vagifem is marketed in 53 countries, having been first approved in Denmark in 1990. A single tablet is inserted in the vagina once daily for two weeks, and then twice weekly as a maintenance dose. The sponsor states that the low dose has low systemic availability, does not stimulate the endometrium and need not be opposed by a progestin.

The sponsor conducted two animal studies. Ten and 28 day studies in rabbits.

Vaginal tolerance test of oestrovag (Vagifem) in rabbits. Novo study No. 2485; 1985.

Twenty one NZW rabbits were divided into three groups of 7 animals. Group 1, two animals untreated and 5 animals manipulated with the applicator. Gp 2, All animals dosed with 5 ug estradiol. Group 3, all animals dosed with placebo. Treatment duration was 10 days.

Results: There was a high incidence of minor bleedings from the vagina just after manipulation with the applicator in all three groups.

Histology was performed on ovaries, uterus and three levels of vagina. There were no effects in the ovaries or uterus. The histology report is vague and difficult to decipher. Basically, the pathologist stated that the treatment with 5 ug estradiol for 10 days did not cause irritation of the vaginal mucosa or underlying tissue. The treated animals showed a high incidence of hyperemia and in some animals minor edema in the vagina. The degree of reaction to the treatment ranged from nil to 10 and the pattern of distribution in the three gps indicates that the inflammatory reaction observed in some animals could have been induced mechanically.

Study to determine the possible systemic toxicity and evaluate the local tolerance of vagifem during repeated intravaginal administration in the rabbit. Centre de Recherches Biologiques. Study No. 920052 E. 1992.

Five gps of 6 NZW rabbits were given Vagifem for 28 consecutive days. Doses were1 tablet per day weighing 20 mg containing 2.50, 6.25 and 15 ug of estradiol. Group 1 was control, gp 2 was given a placebo tablet and gps 3, 4 and 5 were treated with the three doses of estradiol.

Results: There were no effects on clinical signs, body wts (nonsignif increase in two high dose gps), hematology or clinical chemistry.

Histology: No treatment related findings were noted in any non target organs. Macroscopically, there was noted a slight dose-dependent hypertrophy of the uterus compared to controls. There was no sign of treatment related irritation in the vagina. There were treatment related functional changes in the uterine horns including stimulation of glandular growth associated with ciliated cell proliferation and morphologic signs of secretory activity.

Conclusion: Treatment of women with Vagifem results in serum estradiol AUC levels of approximately 500 pg*hr/ml with steadystate Cmax levels ranging from 50 to 80 pg/ml with little systemic toxicity expected (Tables 2-1, 2-3, 2-6). The two animal studies with intravaginal administration of Vagifem revealed no unexpected toxicity to the vagina, uterus or ovaries.

Recommendation: Pharmacology recommends approval of Vagifem for the treatment of atrophic vaginitis.

Labeling: