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APPLICATION NUMBER:NDA 20-870

PHARMACOLOGY REVIEW(S)

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NDA 20-870

Rhone Poulenc Rorer
Pharmaceuticals
Collegeville, PA

Submission dated: 8-7-1997 Received at CDER: 8-7-1997

Pharmacology Review of Original NDA Submission

Drug product's established name: Estradiol/norethindrone acetate
Proprietary name: Aliatis
Code name: RPR 106522

Pharmacological class: estrogens and progestins

Dosage form: Transdermal system

Proposed Strengths: 50 ug E2 and 140 or 250 ug NETA

Route of administration: transdermal

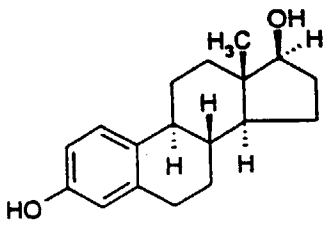
Proposed indications for use:

1. Treatment of moderate to severe vasomotor symptoms associated with menopause,
2. Treatment of vulvar and vaginal atrophy and
3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

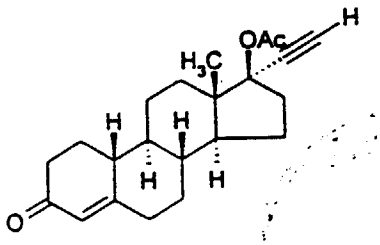
Chemistry of estradiol hemihydrate and norethindrone acetate:

Molecular structure:

Estradiol



Norethindrone acetate



Chemical name:

Estradiol: Estra-1,3,5(10)-triene-3,17B-diol
Norethindrone acetate: 17-hydroxy-19-nor-17a-pregn-4-en-20-yn-3-one acetate.

Molecular formula:

Estradiol: C18 H24 O2 M.W. 272.39
Norethindrone acetate: C22 H28 O3 M.W. 340.47

Estradiol CAS registry number: 50-28-2
Norethindrone acetate CAS registry number: 51-98-9

Drug product composition and dosage form: Aliatis is a adhesive-based patch for combined estrogen/progestin transdermal delivery. Estradiol and norethindrone are uniformly dispersed in a solid adhesive matrix. The patch is intended to be marketed in 2 sizes. A 9 cm^2 size which is designed to deliver 50/140 ug/day E2/NETA and a 16 cm^2 size which delivers 50/250 ug/day. The compositions are listed in table below:

Target delivery rate

Norethindrone acetate(ug/day)
Estradiol(ug/day)

Ingredients-mg/patch(%w/w)

Norethindrone acetate,, USP
Estradiol, USP
Povidone, USP

Silicone adhesive
Acrylic adhesive

Dipropylene glycol

Backing(mg/unit)
Liner(mg/unit)

Total weight(mg/unit)

Patch size(cm^2)	9	16

Related IND: Sponsor's IND

Rationale for the development of Aliatis: It was stated that administration of estradiol and norethindrone via the transdermal route bypasses the rapid first pass metabolism by the liver and by circumventing this first pass effect, smaller total daily doses of these hormones can be delivered transdermally. Advantages of transdermal administration compared to oral formulations include a reduced dose that avoids excessive accumulation of drug in tissues and a sustained and controlled delivery of drug. In addition, it was stated that transdermal delivery of estrogen restores the premenopausal estrone/estradiol balance, minimizes the induction of hepatic protein production, lowers the biliary cholesterol saturation index, provides a predictable absorption profile, reduces gastrointestinal effects and slows the metabolism of the less active estrogens

Nonclinical pharmacology and toxicology:

Both estradiol and noretnindrone acetate are FDA's approved drugs and have been extensively studied with established clinical safety and efficacy.

All nonclinical pharmacology and toxicology reports included in this submission except for reports No.DS96-013 and DS96-014 entitled Acute dermal toxicity of RPR 106522 in rats and rabbits respectively have been reviewed previously under various IND submissions. Copies of these reviews are appended.

For the determination of acute dermal toxicity in rats (No.DS96-013), 4 groups of 10 SD rats were used. Two 14.5 cm^2 patches were applied to the backs of animals in group 2 (placebo patches), group 3 (RPR patches containing a total of 2 mg estradiol and 8.8 mg of NETA) and group 4 (patches containing 8.8 mg NETA). Group 1 animals received no patches. Patches were removed after 3 days.

Results:

There were no deaths or treatment-related clinical signs. Body weight was not affected and no treatment-related gross lesions were observed.

In the rabbit study (No.DS96-014) 4 groups of 8 rabbits (4/s) were used. Six 14.5 cm^2 patches were applied to the dorsal pinnas (3 patches/ear) of animals in groups 2, 3 and 4; placebo patches

to group 2, RPR 106522 patches containing a total of 6 mg of estradiol and 26.4 mg of NETA per animal to group 3 and patches containing 26.4 mg NETA per animal to group 4. Group 1 control animals received no patches. Animals were collared and patches were removed after 3 days as in the rat study.

Results:

There were no deaths observed. Minimum to moderate erythema was noted at application sites in both treated and placebo groups at the end of application period which in most cases was resolved by day 12. There was treatment-related loss in body weight in both males and females with RPR 106522 patch application and in females with NETA patch when compared to placebo patch control animals. It was statistically significant in RPR 106522 treated females. On day 4, the weight gain in group 1 to 4 males were 247.8, -42.8, -117.0 and 30.0 g and for females 145.3, -100.8, -204.3 and -145.0 g respectively. On day 8, weights were comparable to placebo and collared control animals. Food consumption was decreased in RPR106522 treated females compared to collared control placebo animals during the 3 day treatment period. Food consumption was decreased in all collared animals and returned to normal between day 5 and 13. There were no gross lesions seen with the application of either placebo or test article patches.

Previous human experience:

Seven PK studies were conducted to assess the systemic norethindrone, estradiol and estrone exposure from Aliatis 50/140, 50/250 and 50/400. There were 4 supportive studies (101, 102, 103 and 105) to determine the final Aliatis formulation for clinical development and 3 definitive studies (104, 122 and 126) were conducted in healthy postmenopausal women to assess PK of NET, estradiol and estrone during single and multiple patch applications. The PK after long term use were also assessed in the 1 year phase 2 studies (study # 201 with sequential regimen and 202 with continuous regimen) and in the 3 month phase 3 studies (studies 303 and 304).

Clinical studies were designed to investigate following 2 primary efficacy endpoints in studies 201, 202, 303 and 304:

1. The efficacy of 50 ug/day of estradiol when given in combination with NETA on the reduction of vasomotor symptoms and

2. The efficacy of 3 doses of NETA (140, 250 and 400 ug/day) when given in combination with estradiol on the prevention of estrogen-induced endometrial hyperplasia.

Based on the results of clinical studies, sponsor concluded that combination therapy with Aliatis provides excellent control of vasomotor symptoms and reduction of the incidence of endometrial hyperplasia, with fewer side effects and better compliance compared to treatment with estradiol only transdermal delivery system in postmenopausal women with intact uterus.

NETA addition to estrogen reduced significantly HDL-C compared to estrogen treatment alone (-3.1, -9.1 for 0.05/0.14 and 0.05/0.25% Aliatis and +7.3 for 0.05 Vivelle, expressed as % change from baseline). Concomitant decreases in LDL-C (-4.6,-7.4 and -3.4) and in TGs (-4.6, -9.5 and -6.7) were also observed.

Note: In study 122,, it was demonstrated that application of Aliatis on the abdomen resulted in 25-28% greater rates and extents of estradiol and NET absorption compared to buttock placement. Sponsor however, pointed out that reduced bioavailability from application of Aliatis on the buttock would not adversely affect clinical use since competitor products which claim estradiol delivery rate of 50 ug/day, average steady state estradiol serum concentrations range from 32 pg/ml for Estraderm to 57 pg/ml for Vivelle. Values for Climara, Aliatis 50/140 and 50/250 were 33-45, 45 and 50 pg/ml respectively. It was proposed that buttock would offer an alternative wear site which could increase patient compliance.

No differences in PK however, were observed for Climara (Berlex Laboratories) when patch was applied to abdomen or buttock.

It was suggested that combination transdermal product will simplify therapy, ensure adequate endometrial protection, enhance overall compliance and offer a choice of effective and safe regimens.

Proposed text of labeling and patient information leaflet: are similar to other estradiol transdermal systems i.e., Climara (Berlex Laboratories) and Fempatch (Parke-Davis).

Recommendations: Based on review of the preclinical data submitted and extensive clinical experience with Aliatis, Pharmacology considers it safe and recommends approval of NDA 20-870 for the combined estradiol/NETA transdermal systems for the proposed indications.

/S/ 9/16/97

Krishan L. Raheja, DVM, PhD

/S/ 9/17

NDA 20-870
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HFD-580/A.Jordan
HFD-580/K.Raheja, 9-16-1997, N20870.ori