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APPLICATION NUMBER: NDA 20-791

PHARMACOLOGY REVIEW(S)

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NDA 20-791

Alza Corporation
Palo Alto, CA

Submission dated: 12-20-1996 Received at CDER: 12-23-1996

Pharmacology Review of Original NDA Submission

Drug product's established name: testosterone transdermal system

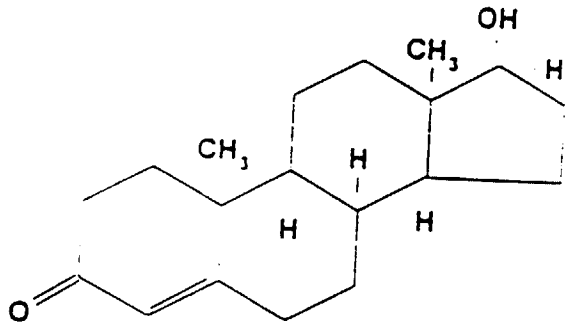
Code names: Testoderm AT, Testoderm -II, Testoderm NS system, TTS testosterone 60 cm and many more.

Alza Code name: 0001732

System's active drug substance: testosterone

Chemical name: 17-B Hydroxyandrost-4-en-3-one

Structural formula:



Empirical formula: C19 H28 O2 Molecular weight: 288.43

Dosage form: transdermal therapeutic system

Route of administration: transdermal

Therapeutic indications: testosterone replacement therapy in males for conditions associated with deficiency or absence of endogenous testosterone.

Related INDs, NDAs and DMFs: INDs NDA 19-762; DMFs

System's components and composition:

Component	Amount/system (mg)
Gel	
Testosterone, USP	
Alcohol, USP, %	
Hydroxypropyl cellulose, HF, NF	
Backing	
Film, polyester/EVA	
Trilaminate	
Film, EVA % VA),	
polyisobutylene	
polyisobutylene	
Film, Siliconized polyester	
Total system wt with protective lining	

All of the system's components have either been previously used in FDA's approved products or are listed in FDA's Inactive Ingredients Guide.

Description of transdermal therapeutic system: TTS is manufactured as a single dosage strength to provide single in-vivo delivery of 6 mg of testosterone per day. The system is a clear thin elliptical unit with a drug delivery area of 60 cm^2.

The occlusive backing film prevents drug and ethanol loss from the system. The drug reservoir contains wt% testosterone in an alcoholic gel. A membrane along with the adhesive layer comprise the rate-control laminate which controls the delivery of testosterone from the system to the skin. Adhesive layer which comprises of polyisobutylene provides attachment of the system to the skin. The protective layer is a Siliconized polyester film that protest the adhesive prior to use.

Rationale for the development of testosterone -II:

It was stated that for testosterone replacement for androgen

deficiency in men with hypogonadism, three most common therapies are as follows:

1) testosterone injections (testosterone enanthate and cypionate),

2) oral alkylated testosterone (methyl testosterone and fluuoxymesterone) and

3) transdermal testosterone (ALZA's Testoderm and TheraTech Androderm).

With injection therapy, ester is rapidly hydrolyzed at the injection site and metabolized, resulting in high testosterone concentrations in the beginning which fall off to baseline levels or lower before next injection.

With oral administration it is hard to achieve full therapeutic androgen replacement as these are weak androgens and also they are reported to produce highly variable testosterone and DHT levels.

Transdermal applications avoid supraphysiologic peaks and variable serum testosterone levels associated with testosterone injections and oral administration. ALZA's Testoderm patch approved under NDA 19-762 is to be applied to the scrotal skin and its delivery is said to mimic the circadian pattern of androgen production as does Androderm patch by TheraTech. Although Testoderm showed distinct advantages over other routes of administration in terms of safety, efficacy, no variations in absorption caused by food intake, no hepatic first pass, presentation of physiologic dose and normal serum testosterone concentrations, ease of discontinuation of dosing and low abuse potential, it was thought not convenient.

Testoderm II is developed to achieve greater product acceptability and avoid scrotal first pass which results in non-physiologic testosterone/dihydrotestosterone ratio because of significant 5-alpha-reduction by 5-a-reductase. DHT is thought to be involved in the pathogenesis of prostatic hyperplasia. Testoderm II TTS is easy to self administer at a comfortable application site on upper buttocks, back or upper arm. As compared to Androderm, it is stated that it offers the convenience of a single patch and presents a low degree of dermal irritation. It is found to be free of phototoxic and photoallergenic skin reactions.

Nonclinical pharmacology, toxicology and metabolism:

The pharmacology, toxicology and metabolism of testosterone is extensively documented in literature and for this submission has been referred to sponsor's previously approved NDA 19-762. However, since the formulation is changed with respect to excipients to enhance the transport of drug across arm and torso skin which is resistant to the permeation of testosterone, sponsor has conducted the following preclinical studies to support safety of Testoderm II:

1. Single dose special toxicity studies:

a. Final report - TR-95-4708-038 Primary skin irritation study on rabbits of TTS (testosterone NS) PET/EVA

b. Final report - TR-95-4708-046 Primary skin irritation study of Transdermal Therapeutic System (TTS) testosterone nonscrotal) on rabbits.

2. Multiple special toxicity studies:

a. Final report - TR-4708-039 Seven day irritation study on rabbits of TTS (testosterone NS) PET/EVA

b. Final report - TR-95-4708-045 Seven day irritation study of Testosterone Therapeutic System (TTS) (testosterone nonscrotal) on rabbits.

3. Sensitization study:

Final report - TR-95-4708-001 Evaluation of the sensitization potential of TTS (testosterone NS) with PET/EVA or backing from Code NO. 000289.

4. Subchronic toxicity study:

Final report - TR-94-4708-002 Twenty-eight day dermal toxicity study on rabbits of TTS (testosterone NS) with PET/EVA backing or backing from Code No. 0002890

5. Research studies:

a. BIO-92-BO19-3702 Primary skin irritation study of isopropyl alcohol gels and ethanol gels and of Transdermal Therapeutic

Systems containing isopropyl alcohol gels and ethanol gels.

b. BIO-89-B037-1550 Evaluation of the effect of sodium dodecyl sulfate on contact sensitization to ethanol in the guinea pig.

All of the above mentioned study results except for guinea pig hypersensitization study, were submitted previously under IND and reviewed on 11-12-1996 and 11-14-1996 respectively. Data on serum testosterone levels and skin histological examination in the rabbit 7 day cumulative irritation study (No TR-95-4708-045) and serum testosterone levels and histopathology of various organs in the 28 day dermal toxicity in rabbits (No TR-96-4708-002) were not included in the draft report. These data is summarized as follows:

In the 7 day study, serum sampled from animals predose, before removal of application 1, and before removal of application 7 had a mean of testosterone level of 4.6 ng/ml, 243.3 ng/ml and 414.5 ng/ml respectively. Histological evaluation of skin treatment sites revealed no significant differences between active and placebo skin sites. Both had mild generally multi-focal acanthosis, hyperkeratosis and chronic dermal inflammation. Mild to moderate these conditions were observed in 3 untreated sites.

In the 28 day dermal toxicity study, there was great variability in serum testosterone levels in males. In females testosterone increased from predose level of ng/ml to a range of ng/ml. Expected effect of treatment with each backing was increased liver and heart weights and decreased testes weight. No microscopic changes were reported in these tissues. Microscopic changes indicative of irritation were similar for active and placebo treated sites but were greater for female compared to male rabbits. In female rabbits, however, the placebos were more irritating than the systems with testosterone.

All studies submitted under IND were unaudited draft reports. However, in the NDA all are final reports and carry statement that studies were conducted in accordance with FDA's GLP regulations.

<u>Results of the guinea pig sensitization study TR-96-4708-001 are summarized below:</u>

Eighty-five Hartley male guinea pigs were in 5 treatment groups to evaluate the potential of 2 different transdermal therapeutic systems (non-scrotal) and controls. Groups 1 to 4 had 20 animals

each while group 5 had 5 guinea pigs.
Animals of group 1 received active TTS with PET/EVA backing while group 2 received placebo system with the same backing. Group 3 received active TTS with backing from Code No. 0002890 and group 4 received placebo with backing as in group 3. Group 5 received % in . All test and placebos were applied under occlusion for 24 hours to the back every 2-3 days for a total of 9 applications over 3 week period. Application sites were scored 2 and 24 hours after removal of the first and 9th application to assess primary and cumulative skin irritation. After second and fourth application, intradermal injections of 2 x 0.05 ml of a sterile water: emulsion were administered to 2 sites in the shoulder region.

After 9th induction application, there was a rest period for 2 weeks, after which for the first challenge, animals in groups 1 and 2 were applied test and placebo TTS with PET/EVA backing. Groups 3 and 4 were applied respective patches with backing from Group 5 animals were topically challenged with % in % and with % (vehicle). Two weeks later they were rechallenged with same dosing regimen. Responses were defined positive if erythema and edema score was greater than 2 at 48 hours after challenge and did not clearly represent irritation.

Results: showed that both active and placebo formulations of TTS with either backing produced mild to moderate irritation after first and last induction application. This was attributed to combined effect of adhesive removal and presence of In the positive control group, 1/5 and 5/5 animals had positive reaction after first and second challenge respectively, confirming that sensitization reaction could be elicited in the animals used in the study.

Previous human experience with Testoderm -II testosterone transdermal system:

The sponsor has evaluated the PK of testosterone using Testoderm -II in hypogonadal patients in 7 studies: 2 pivotal PK studies (C-95-044 and C-950945) and 5 supporting studies. Results of these studies demonstrated the following:

1. Serum testosterone concentrations were proportional to the surface area of Testoderm -II.

2. No appreciable accumulation or changes in drug metabolism

occurred following daily application of the system.

3. No appreciable skin metabolism of testosterone occurred.

4. The system can be placed interchangeably on the upper buttock, the back or the upper arm because serum testosterone concentrations were equivalent after application at these sites.

5. Body weight was a significant factor influencing serum testosterone concentration.

Clinical efficacy and safety, and its potential for abuse were derived from 2 pivotal PK studies, 2 topical safety studies and 3 supporting studies. The results of these studies are summarized below:

1. The system provides a dose of approximately 6 mg of testosterone over 24 hours.

2 Serum concentrations of testosterone, dihydrotestosterone, estradiol and free testosterone were restored to within normal range.

3. It demonstrated circadian rhythmicity and

4. There was no drug depot associated with the use of Testoderm -II testosterone transdermal system.

As regards safety, it was stated that majority of Testoderm -II users do not experience any itching or erythema and these conditions are infrequent; the system application sites do not require daily rotation since cumulative irritation was not observed and moderate erythema during repeated application occurred only occasionally in less than 20% of users; no evidence of phototoxic or photoallergic skin reactions was seen with Testoderm -II; the incidence of contact sensitization was only 0.5%; there were no differences in the incidence of local skin reactions in elderly and other adult subjects and incidence of moderate to severe erythema was statistically significantly lower in subjects using Testoderm -II compared with those using Androderm.

Draft Labeling: A combined draft labeling is given for Testoderm AT (present system for arm/torso application with delivery rate of 6 mg/day), Testoderm (testosterone transdermal scrotal system to deliver 4 or 6 mg testosterone/day) and Testoderm with

adhesive (scrotal system to deliver 6 mg testosterone/day). The labeling is similar to one approved under sponsor's NDA 19-762 for Testoderm (testosterone transdermal system).

Summary: Studies conducted both in animals (study results submitted under IND and in humans demonstrated that the proposed testosterone transdermal system, Testoderm -II is effective for the proposed indication, is well tolerated and poses no unexpected safety concerns.

Recommendations: Based on extensive previous preclinical and clinical experience with Testoderm (testosterone transdermal scrotal system) and on the results of the studies conducted in animals and humans with the proposed testosterone transdermal non-scrotal system, Pharmacology considers it reasonably safe and recommends approval of Testoderm -II for the proposed indication.

2/25/97

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HFD-580/A.Jordan
HFD-580/K.Raheja, 2-25-1997, N20791.ori

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