CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-791

ADMINISTRATIVE DOCUMENTS

SECTION 1. INDEX

F. Patent Declaration

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of Testoderm®-II. This product is the subject of this application for which approval is being sought.

PATENT NUMBER	TYPE	EXPIRATION DATE	OWNER
4,379,454	Formulation and method of use	February 17, 2001	ALZA Corp.

Typed Name: Steven F. Stone

Title: Director of Intellectual Property

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-791 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF 550 Trade (generic) name/dosage form: Testoderm TTS (testosterone transdermal system) 5mg/day Action: (AP) AE NA

Applicant Alza Corp. Therapeutic Class 35

Indication(s) previously approved hypogonadism Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application hypogonadism (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

X 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Gerri G Troendle PM 12/4/97

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 20-791
HF 550 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

SECTION 1. INDEX

H. Debarment Statement

ALZA hereby certifies that it has not utilized the services of any firm or person(s) debarred in accordance with the Federal Food, Drug and Cosmetic Act [FDC Act § 306(k)] in the preparation of information for this NDA.

Janne Wissel
Vice President, Quality Management & Regulatory Affairs

Group Leader Memorandum

NOV-17 1997

NDA:	**20-791**
Drug and indication:	**Testoderm® TTS (testosterone transdermal patch)**
Dose:	**one or two 5 mg patches applied once daily to the arm, back or buttocks**
Applicant:	**Alza Corporation**
Submission dated:	**December 26, 1996**
Date of MO review:	**September 1, 1997 (draft)**
Date of Memorandum:	**December 17, 1997**

In this application, the sponsor requests approval for a nonscrotal transdermal system for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Of note, the sponsor currently markets two scrotal systems, Testoderm® and Testoderm® with Adhesive. The efficacy of this product is supported by two open-label, short-term pharmacokinetic studies [protocols C-95-044 (bioavailability relative to Testoderm®) and C-9504-045 (comparison of three application sites)] conducted in a total of 36 hypogonadal men. These studies together suggested that a single patch provided physiologic levels of testosterone replacement for most men studied (94%), and that application to the upper buttocks, upper arm, and the back was clinically similar. Safety and local skin tolerability are further supported by a study conducted in 76 hypogonadal men with a one-month treatment exposure to each of Testoderm® TTS and Androderm® products (protocol C-96-005) and by additional studies conducted in normal volunteers.

I concur with the recommendation of the primary reviewers that this application is approvable. Notable issues at the time of this memorandum include:

1. **Stability**

The proposed two-year shelf-life was found unacceptable because of the unanticipated finding of lower than expected bioavailability in a study conducted in eight men treated with "aged" patches (protocol C-96-048). As reflected by internal meeting minutes, reviews by the CMC and biopharmaceutics reviewers and the sponsor's letter dated November 26, 1997, it was determined that an eighteen month shelf-life could be allowed, provided that the sponsor agreed to a phase IV commitment to conduct a clinical study Agreement with the sponsor on this issue has been reached.

2. **Clinical implications of DSI audit findings**
As noted in the biopharmaceutics review, audit by the Division of Scientific Investigations uncovered problems with sample handling and analytic procedures for some parameters (specifically, for free testosterone, dihydrotestosterone and estradiol). As a result of these findings, no pharmacokinetic evaluation has been performed for these analyses. However, these deficiencies did not have a significant impact on the clinical review (and approvability) of this application because assays for total testosterone, the primary pharmacokinetic parameter, were felt to be acceptable (with the exception of data for one patient).

3. **Labeling**
The draft labeling of December 3, 1997 was generally acceptable except for the need to make minor editorial changes and to eliminate clinical trial data (protocol C-96-005) that compared the incidence of local skin reactions between Testoderm® TTS and Androderm®. This study and a smaller comparative study do not support the sponsor's claim of better local tolerability because of their open-label design, infrequent assessment of skin sites and lack of photographic documentation to verify the findings. These comments were communicated to the sponsor in a facsimile on December 10, 1997 and agreed to in a teleconference on December 15, 1997. With the changes discussed in this teleconference, labeling is now acceptable.

There are no other outstanding regulatory issues.

Heidi Jolson 12/17/97
Heidi M. Jolson, M.D., M.P.H.
Deputy Division Director, HFD-580

cc:
NDA20-791
HFD-580/LRarick/MHirsch/HJolson

c:\h\20791.gl

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-791

NOV 25 1997

Alza Corporation
Attention: Ms. Janne Wissel
Vice President, Quality Management and Regulatory Affairs
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Dear Ms. Wissel:

Please refer to your pending December 19, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testoderm™ TTS (testosterone transdermal system).

We also refer to your amendments dated July 3, August 26, September 12, October 14 and November 3, 1997, in which you provided revised proposed labeling for the pouch, carton, demonstrator patch pouch, and system print mat text and Chemistry amendments.

We have completed our review of the Chemistry, Manufacturing and Controls and proposed Labeling sections of your submission and have identified the following deficiencies:

[redacted]

1. A dimension specification for the drug product should be adopted.

2. According to the ICH guideline, any degradation product above % in the drug product must be reported.

3. The specification for the drug product is too wide, based on the stability data. The specification should be tightened or a rationale provided for the current specification.

4. The USP IR identity test should be conducted as part of the acceptance of the testosterone drug substance from the supplier along with the certificate of analysis.

5. The *in vitro* release rate should be set based on 18 months stability data since the tentative expiration date is 18 months.

6. The DMF for Adhesive trilaminate was reviewed separately. The DMF holder was notified of the deficiencies.

[redacted]

1. The term appears in multiple sections. Since the studied sites of application were actually the arm, upper buttocks or back, the term should be removed and replaced with the terms in all appropriate locations throughout the proposed label.

2. By mutual agreement, the tradename has been changed to TESTODERM™ TTS. Therefore, the tradename TESTODERM™ TTS should appear in all appropriate locations throughout the label in lieu of

3. The proposed daily dose for Testoderm™ TTS was mg. This dose should be changed to mg/day throughout the labeling as agreed to in the November 21, 1997, teleconference.

[redacted]

DESCRIPTION section:

1. The last sentence of the first paragraph reads, . This sentence should be moved

subsection.

2. A brief explanation should preface the product information table.

CLINICAL PHARMACOLOGY section:

1. In the **Testosterone** subsection, the third sentence should read as follows:

2. In the **Pharmacokinetics, Absorption** subsection for Testoderm™ TTS, should be replaced with the attached

3. In the **Geriatrics** subsection, the final sentence reads This information does not refer to clinical pharmacology data and should be removed from this section. If clinically important, this information should be presented as specific incidence rates in the **ADVERSE REACTIONS** section.

4. In the **Clinical Studies** subsection, under the results of pivotal studies C-95-045 and C-95-044 should be presented in a clear and concise manner as follows:

5. In the **Clinical Studies** subsection, under all references to should be removed.

6. In the **Clinical Studies** subsection, under references to the should be removed and presented in tabular format in the **ADVERSE REACTIONS** section.

7. In the **Clinical Studies** subsection, under the sponsor should remove paragraphs 3 and 4, and Table A. The data in this section is derived from two open-label studies which do not support this comparison.

CONTRAINDICATIONS section:

The second sentence should be changed to read

WARNINGS section:

1. The five (5) warnings should be listed numerically (1 through 5) and should be separated as follows:

2. Reference is made to the *frequent* occurrence and *occasional* persistence of gynecomastia in patients being treated for hypogonadism. If possible, the specific incidence rates of transient and persistent gynecomastia during treatment should be noted.

PRECAUTIONS section:

1. In the **Laboratory Tests** subsection, serum testosterone should be included as a recommended laboratory test and placed first in the present numerical order. The serum testosterone testing recommendation that is made in the **DOSAGE and ADMINISTRATION** section should be reiterated.

2. In the **Pregnancy Category X** subsection, the recommendation should be changed to read as follows:

3. In the **Nursing Mothers** subsection, the recommendation should be changed to read as follows:

4. In the **Pediatric Use** subsection, the sentence should read as follows:

ADVERSE REACTIONS section:

1. The first two sentences of the first paragraph may remain but the remainder of the paragraph, which refers to should be removed.

2. Under subsection, of the total 435 participants in clinical studies, the number of hypogonadal males (N=) versus healthy adult male volunteers (N=) should be specified. Additionally, the range of treatment duration should be specified.

3. Under , the listed adverse reactions are noted to be This phrase should be removed. All adverse reactions should be listed regardless of causality.

4. Under the percentage of detachments of systems during regular daily activity and during exercise should be described if noted in the clinical studies.

5. Under the adverse effects noted in 104 patients using the product for up to three years should be listed without reference to causality. Therefore, the phrase should be removed.

6. Under the adverse events noted in the referenced study and all other studies which include the product, should be listed by specific incidence rates.

7. The heading should be changed. Since these adverse events may occur with all forms of androgen replacement therapy the heading should read as follows:

DOSAGE and ADMINISTRATION section:

Under patients are instructed to re-apply a new system The sponsor should specify when the re-application of a new system is necessary.

HOW SUPPLIED

1. The established name should be revised to read "testosterone transdermal system."

2. The following storage condition should be added:

[redacted]

1. On the **Backing Label**, the established name should be revised to read "testosterone transdermal system" and the delivery rate "5 mg/day" should be included.

2. **The Pouch and Carton** should be revised to include the following storage condition: In the inactive ingredient list, should be revised to read '

3. On the **Pouch and Carton**, the logo in the tradename should be deleted.

We would appreciate your prompt written response so that we can continue our evaluation of your NDA.

If you have any questions, please contact Terri F.Rumble, B.S.N., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

11/25/97

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-791
HFD-580/Div. Files
HFD-580/CSO/T.Rumble
HFD-580/Rarick/Jolson/Hirsch/Mitra/Rhee/Raheja/Jordan
HFD-870/Dorantes/Haidar
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: Rumble/November 17, 1997/20791ir.002
Initialed by: Rarick,11.25.97/Jolson,11.25.97/Hirsch,11.18.97/Mitra11.18.97/Rhee,11.18.97
/Haidar,11.24.97/Dorantes11.24.97/Pauls,11.18.97
final: Rumble,11.25.97

INFORMATION REQUEST (IR)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-791

JUL 30 1997

Alza Corporation
Attention: Janne Wissel
Vice President, Quality Management and Regulatory Affairs
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Dear Ms. Wissel:

Please refer to your pending December 19, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testoderm™ AT (testosterone transdermal system).

We also refer to your amendments dated February 14, March 10, and July 3, 1997.

We have completed our review of the Microbiology sections of your submission and have identified the following deficiencies:

1. The submission was reviewed for microbiological issues concerning microbiological integrity. In regard to microbial limits, the product does have microbiocidal properties, probably due to in the product. However, this does not obviate the need to establish microbial limits for the product. Interestingly, bacterial spores may be stored in solutions . Other microbes are also capable of adapting to, and contaminating very inhospitable environments.

   Accordingly, microbial limits should be set in a manner such that excursion above the limits may be indicative of process deviations. It will be necessary to use the established microbial limits as product release criteria. After generating a sufficient body of data indicating that microbial limits are unlikely to be exceeded, it may be possible to submit a supplemental application to reduce or eliminate testing.

2. In regard to microbial monitoring of stability samples, microbial limits should be monitored as a portion of the drug product stability protocol. After generating a sufficient body of data indicating that microbial limits are unlikely to be exceeded, it may be possible to submit a supplemental application to reduce or eliminate testing.

We would appreciate your prompt written response so that we can continue our evaluation of your NDA.

If you have any questions, please contact Terri F.Rumble, B.S.N., Regulatory Health Project Manager, at (301) 827-4260.

Sincerelv.

7-28-97

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-791
HFD-580/Div. Files
HFD-580/CSO/T.Rumble
HFD-580/Rarick/Jolson/Fourcroy/Mitra/Rhee/Raheja/Jordan
HFD-160/Stinavage/Cooney
HFD-870/Dorantes/Jarugula
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: Rumble/July 25, 1997/20791ir.001
Initialed by: Jolson,7.28.97/Stinavage,7.28.97/Cooney,7.28.97
final: Rumble,7.28.97

INFORMATION REQUEST (IR)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-791

DEC 31 1996

ALZA Corporation
Attention: Ms. Janne Wissel
Vice President, Quality Management & Regulatory Affairs
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Dear Ms. Wissel:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Testoderm® AT (testosterone transdermal system), 6 mg/day
Therapeutic Classification:	Standard
Date of Application:	December 19, 1996
Date of Receipt:	December 23, 1996
Our Reference Number:	20-791

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 21, 1997, in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact:

Terri F. Rumble, B.S.N.
Regulatory Health Project Manager
Telephone: (301) 827-4260

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours.

12/31/96

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-791
HFD-580/Div. Files
HFD-580/CSO/
HFD-580/Jolson/Fourcroy/Jordan/Raheja/Rhee/Mitra/Dorantes/Barnette/Kammerman
DISTRICT OFFICE

drafted: Rumble/December 31, 1996/20791.ack
Final:

ACKNOWLEDGEMENT (AC)