CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-015

PHARMACOLOGY REVIEW

Cokugh 10

DEC - 8 1999

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: androgel, testosterone
Reviewer Name: Alex Jordan
Division Name: DRUDP
HFD# 580
Review Completion Date: 12/8/99

Review number: 1
IND/NDA number: 21-015
Serial number/date/type of submission: 000/4/28/99
Information to sponsor: Yes ( ) No (X)
Sponsor (or agent): Unimed Pharmaceuticals
Manufacturer for drug substance: ————

Drug:

Code Name: T-Gel
Generic Name: testosterone gel
Trade Name: Androgel
Chemical Name:
CAS Registry Number: 58-22-0
Molecular Formula/ Molecular Weight:
Structure:

Relevant INDs/NDAs/DMFs: IND ———— DMF ———

Drug Class: steroid

Indication: Hormonal replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

Clinical formulation: Testosterone USP, isopropyl myristate NF, alcohol, carbomer 940 NF (a high-molecular weight polymer of acrylic acid cross-linked with allyl ethers of sucrose), ———— water.

Route of administration: Topical gel. Androgel contains 1% testosterone and a daily application of Androgel 5 g or 10 g delivers 50 mg or 100 mg of testosterone. Both doses deliver sufficient testosterone to raise serum levels to within the normal range.

Proposed clinical protocol or Use: see indication

PHARMACOLOGY: The pharmacology of testosterone is well known and has been documented in the literature.

TOXICOLOGY:

General Comments: There were two nonclinical studies in this submission. Testosterone is an approved drug administered by injection or patch, no additional safety information was requested.

Study Title: Acute dermal irritation in rabbits
Study No: —— No.14039
Amendment #, Vol #, and page #: 1.5 pg 5-265
Conducting laboratory and location: ————————

Date of study initiation: completion 7/8/96
GLP compliance: Yes
QA- Report Yes (X) No ()
Methods:
Dosing:

- species/strain: male New Zealand White rabbits
- #/sex/group or time point: 3 males/gp
- age:
- weight: 2.2 kg
- satellite groups used for toxicokinetics or recovery: No
- dosage groups in administered units: placebo gel and 1% testosterone in gel
- route, form, volume, and infusion rate: 0.5 ml of gel applied to 6 cm of normal left flank and scarified right flank. Area is covered by gauze and maintained for 4 hrs. Cutaneous irritation was evaluated at 24, 48 and 72 hrs after application.

Key Study Findings: Dermal irritation was scored for erythema and edema. There was no difference between testosterone gel and placebo gel in dermal irritation at 24, 48 or 72 hrs.

Study Title: Skin sensitization test in guinea pigs
Study No——No.14040
Amendment #, Vol #, and page #: 1.5 pg 5-300
Conducting laboratory and location: ——————————
Date of study initiation: completion 9/4/96
GLP compliance: Yes
QA- Report Yes (X) No ()
Methods:
Dosing:

- species/strain: Dunkin-Hartley guinea pigs
- #/sex/group or time point: 5/s/gp
- age: 3 months
- weight: 344 g/males; 340 g/ females
- satellite groups used for toxicokinetics or recovery: no
- dosage groups in administered units: 1% testosterone, USP
- route, form, volume, and infusion rate: Delayed contact sensitization was evaluated according to the modified maximization method of Magnusson and Klingman and to O.E.C.D. guideline (No 406, 17 July, 1992). Induction phase by intradermal and cutaneous routes. Intradermal route: On day 1, 4 injections were made deep into the dermis of a clipped area in the dorsal region between the shoulders. Animals of both gps received two injections of 0.1 ml of Freund's complete adjuvant diluted at 50% with saline. Cutaneous route: On day 1, the same test site was treated with 0.5 ml of the test substance or placebo and covered by an occlusive dressing for 48 hrs. On day 7, the scapular area was clipped and the animals were treated with 0.5 ml of sodium laurylsulphate to induce local irritation. On day 8 a topical application to the injected area was performed. On day 22, test substance or placebo was applied dermally as a challenge. After 24 hrs, the substance was removed and the area scored 24 and 48 hrs later.
- Drug, lot#, radiolabel, and % purity: lot E620

Results: No cutaneous reactions attributable to the sensitization potential of Androgel were observed.

Key finding(s):OVERALL SUMMARY AND EVALUATION:

Introduction: Testosterone Gel is non-irritating and has little or no sensitizing potential

Safety Evaluation: The only safety concern raised by the initial IND pharm/tox review was the risk of virilization of the female partner and masculinization of the fetus if the woman was pregnant. Sponsor has addressed those concerns with clinical trials looking at the potential for testosterone absorption by female partners of men using the T-gel. Results were mixed but the risk to women and fetuses seems low, especially if the alcoholic gel is allowed to dry. These issues are addressed in the label.
Clinical Relevance of Safety Issues: Potential for virilizing female sexual partners and masculinizing fetuses of pregnant women who come in close contact with men using T-gel.
Other Clinically Relevant Issues:
Conclusions: Issues have been addressed.

Communication Review:

- Labeling Review (NDA): The label conforms to class testosterone labeling. There are no data on testosterone doses for the carcinogenicity studies.

RECOMMENDATIONS: I recommend approval of NDA 21-015, Androgel for testosterone replacement therapy.

Internal comments: None

Reviewer signature/team leader signature [Concurrence/Non-concurrence]

/S/ 12/8/99

cc: list
NDA 21-015
HFD-580
AJordan;

/S/