

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-788

PHARMACOLOGY REVIEW(S)

**Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)**

NDA 20-788 (000-BP)

Date Submitted: November 5, 1997
Date CDER Received: November 6, 1997
Date Assigned: November 18, 1997
Number of Volumes: 1

Drug: Finasteride (Propecia)- 1 mg tablets

Sponsor: Merck & Co., Incorporated
Sumneytown Pike
West Point, PA 19486
(610) 397-2310

Indication: For the treatment of male pattern baldness (androgenic alopecia) and to prevent further hair loss

Related Submissions: NDA 20-180, IND , and IND

Introduction:

With this submission, the Sponsor is responding to a request for more information made by the Agency on October 22, 1997 (via telefax). The request was for the Sponsor to clarify the use of AUC values instead of Cmax in calculating the margins of human safety.

FDA Comment:

The Agency would like to have all comparisons between non-clinical findings and potential human outcomes based on exposure equivalents instead of dose equivalents. In order to establish the most appropriate comparisons, please provide the Agency with approximate multiples of human exposure based on both calculated AUC and Cmax values for animals (Study Numbers: TT #86-058-0, TT #87-114-0; TT #87-016-0, TT#87-016-1; TT #86-057-0; TT #87-704-0; TT #94-9014). Please comment on whether Cmax or AUC(free) would be more appropriate based on the fact that the drug binds tightly to the enzyme, modified, and then released. Also, please clarify whether the calculated AUC values are for the combined bound and free finasteride or just unbound finasteride.

Sponsor's Response:

Because of the time-dependent nature of the inhibition in human type 1 and 2, monkey type 1 and 2, and rat type 2 5 α -reductase, the degree of enzyme inhibition is dependent on the time-integrated exposure of the enzyme to finasteride. For this reason, the Sponsor stated that AUC would be a better measure of the time-integrated exposure than Cmax. The Sponsor also stated that the calculated exposure margins are conservative estimates because the relative

exposure of humans to the free fraction of drug is lower than for rats and dogs. This is because AUC and Cmax values for non-clinical species and humans were determined for total (bound and unbound) drug and because plasma protein binding in humans is higher (90%) than in non-clinical species, rats and dogs (80%).

The AUC and Cmax values for each species is provided in Table 1. The exposure margins are comparable, in most cases. Using AUC values would provide a greater safety margin than using the Cmax values. However, a good safety margin is still obtained when using the Cmax values.

| Species/Sex | Study No. | Drug Week | Oral Dose (mg/kg/day) | AUC _{0-24 hr} (µg·hr/ml) | Cmax (µg/ml) | Exposure Ratio (Cmax) | Exposure Ratio (AUC) |
|-----------------|-----------|-----------|-----------------------|-----------------------------------|--------------|-----------------------|----------------------|
| Rat (male) | 86-058-0 | 52 | 20 | 11.94 | 1.82 | 198 | 240 |
| Rat (male) | 86-058-0 | 52 | 40 | 15.44 | 1.92 | 209 | 312 |
| Rat (male) | 87-114-0 | 14 | 80 | 24.42 | 4.78 | 520 | 488 |
| Rat (male) | 87-114-0 | 14 | 160 | 44.31 | 7.41 | 805 | 888 |
| Rat (female) | 87-114-0 | 14 | 320 | 109.51 | 12.29 | 1336 | 2192 |
| Mouse (male) | 87-116-0 | 13 | 250 | 91.01 | 10.8 | 1174 | 1824 |
| Dog (male) | 86-057-0 | 52 | 45 | 140.48 | 11.4 | 1239 | 2808 |
| Rabbit (male) | 87-704-0 | 11 | 80 | 217.20 | 20.21 | 2197 | 4344 |
| Monkey (female) | 94-9014 | - | 2 | 1.34 | 0.24 | 26 | 27 |
| Human (male) | | 2.5 | 1 mg/day | 0.05 | 0.0092 | - | - |

Conclusion:

No action indicated.

12/1/97

Javier Avalos, Ph.D.
Toxicologist

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cc:
NDA 20-788
HFD-540
HFD-540/Pharm/Avalos
HFD-540/Pharm/Jacobs
HFD-540/CSO/Kozma-Fornaro
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For Concurrence Only
HFD-540/DD/JWilkin
HFD-540/Team Leader/Jacobs *12/12/97*
12/12/97

SEP 29 1997

Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)

NDA 20-788 (000)

Date Submitted: December 20, 1996

Date CDER Received: December 20, 1996

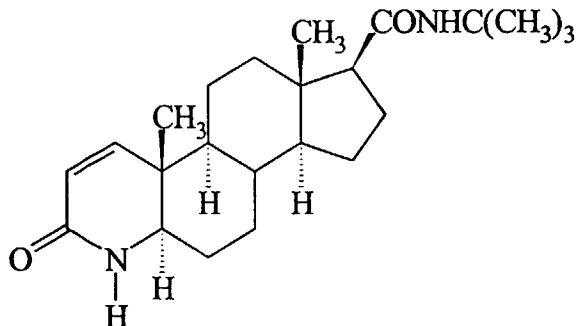
Date Assigned: January 3, 1997

Number of Volumes: 62

Drug: Finasteride (Propecia)- 1 mg tablets

Chemical Name: N-(1,1-dimethyl ethyl)-3-oxo-4-aza-5alpha-androst-1-ene-17beta-carboxamide

Chemical Structure:



Molecular Weight: 372.55

Molecular Formula: $C_{23}H_{36}N_2O_2$

CAS Number: 98319-26-7

Drug Category: anti-androgen

Sponsor: Merck & Co., Incorporated
Sumneytown Pike
West Point, PA 19486
(610) 397-2310

Indication: For the treatment of male pattern baldness (androgenic alopecia) and to prevent further hair loss.

Composition: 1 mg tablet with no novel inactive ingredients.

Route of Administration: Oral

Mechanism of Action: inhibitor of 5 alpha-reductase, an enzyme which converts testosterone to dihydrotestosterone.

Related Submissions: NDA 20-180, IND , and IND

Background: A 5 mg tablet of finasteride (Proscar) was approved for the treatment of benign prostatic hyperplasia in 1992 (NDA 20-180). All acute, subchronic, chronic, reproductive toxicity, and genotoxicity studies are cross-referenced to NDA 20-180. The proposed NDA for the treatment of male pattern baldness is for the approval of a 1 mg tablet of finasteride.

Index of Studies:

All non-clinical studies (pharmacokinetics, pharmacology, toxicology, and reproductive toxicity) were included in the INDs (IND IND) and NDA (NDA 20-180). Pharmacology/Toxicology reviews are appended. The reviews appended evaluated the following studies:

A. Pharmacology

1. The effect of finasteride, a 5 α -reductase inhibitor, on scalp skin testosterone and dihydrotestosterone concentrations in patients with male pattern baldness. Dallob, AL, Sadick, NS, Unger, W, Lipert, S, Geissler, LA, Gregoire, SL, Nguyen, HH, Moore, EC, and Tanaka, WK.
2. The effects of finasteride (Proscar) on hair growth, hair cycle stage, and serum testosterone and dihydrotestosterone in adult male and female stump-tail macaques (*Macaca arctoides*). Rhodes, L, Harper, J, Uno, H, Gaito, G, Audette-Arruda, J, Kurata, S, Berman, C, Primka, R, and Pikounis, B. *Journal of Clinical Endocrinology and Metabolism*, 1994;79:991-996.
3. Other pharmacological studies have been previously reviewed in the NDA and IND application for Proscar (finasteride) (NDA 20-180 & IND

B. Absorption, Distribution, Metabolism, and Excretion

1. Pharmacokinetics and ADME studies have been established in monkeys, rats, dogs, and humans. These studies have been reviewed in the NDA application of finasteride (NDA 20-180).
2. MRL Report: Physiological disposition of finasteride in dogs after oral administration of [¹⁴C]finasteride at 80 mg/kg. August 20, 1996.

C. Toxicology Studies

1. Acute toxicity studies in rats, mice, and dogs (TT #85-2717, 85-2718, 85-2727, 85-2730, 85-2765, 88-9810, 88-9907, 88-9913, 88-9811, and 88-980)
2. 14-Week oral toxicity study in rats (TT #85-005-0).

3. 27-Week oral toxicity study in rats (TT #86-030-0).
4. 53-Week oral toxicity study in rats (TT ##86-058-0).
5. 14-Week oral toxicity study in dogs (TT #85-9017).
6. 27-Week oral toxicity study in dogs (TT #86-029-0).
7. 53-Week oral toxicity study in dogs (TT #86-057-0).
8. 16-Day intravenous toxicity study in dogs (TT #88-630-0).
9. Local Irritation study (Paw-licking response) in rats (TT #88-2744).

D. Reproductive and Developmental Toxicology Studies

1. Oral range-finding in pregnant rats (TT #87-703-1).
2. Oral range-finding in pregnant rats (TT #87-703-2).
3. Critical period study in pregnant rats (TT #87-703-3).
4. Oral teratology study in rats (TT #87-703-0).
5. Oral range-finding study in non-pregnant rabbits (TT #87-702-2).
6. Oral range-finding study in pregnant rabbits (TT #87-702-1).
7. Oral developmental toxicity in rabbits (TT #87-702-0).
8. Segment I Male rat fertility study (TT #86-718-0).
9. Male rat fertility study in immature rats (TT #86-718-1).
10. Male fertility study in mature males (T #86-718-2).
11. Oral fertility study in male rats (TT #87-902-8).
12. Oral fertility study in male rabbits (TT #87-704-0).
13. Oral fertility study in female rats (TT #87-711-0).
14. Oral developmental toxicity study in rats (TT #87-703-7).
15. Postnatal developmental toxicity study in rats (TT #88-900-3).
16. Oral late gestation and lactation study in rats (TT #88-901-8).
17. Effect of 5 α -reductase inhibitors on embryonic and fetal development in Rhesus macaques (*Macaca mulatta*) [TT#94-9014].

E. Carcinogenicity Studies

1. 14-Week dose-range finding study in mice (TT #87-160,-1).
2. Eighty-three week oral carcinogenicity study in mice (TT #87-091-0).
3. 13-Week oral range-finding study in rats (TT #86-100-0).
4. 105-Week oral carcinogenicity study in rats (TT #87-098-0).

F. Mutagenicity Studies

1. Microbial mutagenesis assay (TT #85-8043).
2. V-79 mammalian cell mutagenesis (TT #86-8502, 8608504, 86-8507).
3. In vitro alkaline elution/rat hepatocyte assay (TT #86-8403, 86-8429).
4. Chromosomal aberrations in CHO cells (TT #87-8626, 87-8627, 87-8628).
5. Assay for chromosomal aberrations in mouse bone marrow (TT #88-8600, 88-8601).

Recent Studies Submitted for Review:

A. Pharmacology

1. Identification and selective inhibition of an isozyme of steroid 5 α -reductase in human scalp. Harris, G., et al. *Proceedings of the National Academy of Sciences USA* 1992;89:10787-10791.
2. Mechanism of inhibition of human type 1 and 2 5 α -reductases by finasteride. MRL, September 22, 1994 (revised August 17, 1995).
3. Mechanism-based inhibition of human steroid 5 α -reductase by finasteride: Enzyme catalyzed formation of NADP-dihydrofinasteride, a potent bisubstrate analog inhibitor. Bull et al., *J. Amer. Chem Soc* 1996;118:2359-2365.
4. Mechanism of inhibition of human type 2 5 α -reductase by metabolites of finasteride. MRL, September 22, 1994.
5. Inhibition of rat type 1 and 2 5 α -reductases by finasteride and dihydrofinasteride. MRL, September 22, 1994.
6. Inhibition of dog prostate 5 α -reductase by finasteride and dihydrofinasteride. MRL, September 22, 1994.
7. Characterization of the the isozymes of 5 α -reductase in rhesus prostate and skin. MRL, March 28, 1994.
8. Expression of 5 α -reductase in rhesus fetal tissues. MRL, September 8, 1995.
9. Cloning and expression of rhesus monkey types 1 and 2 5 α -reductase. MRL, July 7, 1996.
10. Immunolocalization of types 1 and 2 5 α -reductase in the human scalp. MRL, July 7, 1996.
11. Bioactivity of the metabolites of finasteride. MRL, May 30, 1996.

Summary of Studies:

Pharmacology -

The pharmacology of finasteride has been examined and well characterized. This compound is a specific inhibitor of 5 α -reductase, the enzyme which converts testosterone to dihydrotestosterone. Two distinct isozymes are found in mice, rats, monkeys, and humans: Type 1 and 2. Each of these isozymes are differentially expressed in tissues and developmental stages. In humans, type 1 5 α -reductase (5 α R) is the predominantly isoform in the sebaceous glands of most regions of skin and is also found in the liver. The type 2 5 α R isoform is primarily found in prostate, seminal vesicle, epididymis, and granular layer of the infrainfundibular region and root sheath of the hair follicle. Type 2 is also present in the liver. During development, type 1 isoform is detected in human fetal skin at gestational ages of 16 to 21 weeks and in newborn liver and scalp. Detection of type 1 is lost around age 3 and not detected until puberty in scalp. The type 2 isoform is also present in prostate and genital skin of human fetuses.

Although both isoforms of 5 α R are found in the scalp region, finasteride specifically inhibits the type 2 isoform. Using native tissue (scalp and prostate), binding studies examining the potential of finasteride to inhibit either isoform revealed a 100-fold selectivity for the human type 2 5 α R over the type 1 isoform (IC₅₀ = 500 and 4.2 nM for type 1 and 2, respectively). A greater selectivity of 300-fold was observed with cloned isozymes.

Additionally, the half-life of finasteride dissociation for the type 2 isoform was 31 days (determined by monitoring the release of ^3H from human type 2 $5\alpha\text{R}$ inactivated with ^3H -finasteride). The material released from the enzyme was determined to be the dihydrofinasteride compound. The half-life for the type 1 isoform was 14 days. Steady-state dissociation constants for each isozyme is 0.18 nM and 1 pM for type 1 and 2, respectively.

Mechanistically, finasteride inhibits both isozymes virtually identically. In both cases, the inhibition by finasteride is accompanied by the reduction of the inhibitor to dihydrofinasteride and adduct formation with NADP^+ . However, the concentration of finasteride required to inhibit the human type 1 isozyme is far greater ($\text{IC}_{50} = 670 \text{ nM}$) than that required for the type 2 form ($\text{IC}_{50} = 4 \text{ nM}$). The metabolic products of finasteride (ω -hydroxy finasteride and ω -oic acid finasteride) also selectively inhibited the human type 2 isozyme ($\text{IC}_{50} = 10$ and 40 nM , respectively). Inhibition of the type 1 isozyme by the metabolic products was observed with concentrations greater than 1000 nM .

Similar inhibitory mechanisms were also suggested in rat and dog $5\alpha\text{R}$ isozymes. Both isozymes are also present in these two species. However, the amino acid homology of the rat isozymes to human enzymes is 60% and 77% for the type 1 and 2 isoforms, respectively. Furthermore, isozyme distribution in rats differs to human distribution. More importantly, finasteride is a potent inhibitor in both isozymes of the rat ($\text{IC}_{50} = 13 \text{ nM}$ and 1 nM for type 1 and 2, respectively). Thus, any biological activity observed in the rat studies is due to the inhibition of both isozymes of $5\alpha\text{R}$. In the dog, finasteride was a modest inhibitor of $5\alpha\text{R}$ in dog prostate with an IC_{50} of 3-3.6 μM for either isozyme.

A better animal model is the rhesus monkey. A greater amino acid homology to the human $5\alpha\text{R}$ isozymes is observed in cynomolgus monkey type 1 and 2 isozymes (93-95%). In addition, both isoforms demonstrated similar characteristics with respect to affinities and mechanism of inhibition of finasteride. The IC_{50} values for finasteride was 780 nM and 17 nM for the cloned rhesus monkey type 1 and 2 $5\alpha\text{R}$, respectively. This corresponds to a 40-fold selectivity of the type 2 isozyme over type 1 by finasteride. Furthermore, the tissue distribution of the rhesus types 1 and 2 $5\alpha\text{R}$ are also similar to the human distribution. In rhesus fetal tissue, type 1 is present in scalp, back skin, brain, liver, and testis. While for the type 2 isozyme, the enzyme is present in prostate, external genitalia, seminal vesicle, kidney, mammary skin, and scrotal skin.

As to the efficacy of finasteride, the administration of finasteride to humans or finasteride results in a significant decrease (60-70%) in serum dihydrotestosterone. In turn, the DHT decrease causes a decrease in prostate size and increases hair growth in animals. Administration of 1 mg/kg/day of finasteride to male and female stump-tail macaque can increase mean hair weight and significantly increase hair follicle length.

Pharmacokinetics-

From the reviews of previous submissions, the biopharmacokinetics of finasteride was examined in monkeys, dogs, rats, and humans. Table 1 compares the pharmacokinetic values obtained for rat, dog, monkey, and man following a single oral administration. The pharmacokinetic values represented for man at a dose of 5 mg/day were obtained following an administration of a 5 mg tablet, five 1 mg tablets, or five 1 mg capsules. Pharmacokinetic data

are also available in humans following an oral administrations of 38, 50, 200, and 400 mg. Following a single of administration of finasteride, a good correlation between drug plasma AUC values and dose administered is observed. Table 2 contains pharmacokinetic data for animals and humans treated with multiple doses of finasteride. In humans, a dose of 1 or 5 mg per day was given for 17 days. Based on the ratio of Day 17 AUC values to Day 1 AUC values, a modest accumulation of finasteride (35% and 47%) in plasma is observed after 17 days of 1 or 5 mg/day, respectively.

Table 1. Comparative pharmacokinetics of finasteride following a single oral administration.

| Species | Dose | C _{max} (ug/ml) | T _{max} (hours) | T _{1/2} (hours) | AUC ^a (ug*hr/ml) | F ^b (%) |
|---------|---------------------|--------------------------|--------------------------|--------------------------|-----------------------------|--------------------|
| Rat | 5 (mg/kg) | 0.30 | 1 | 1.7 | 0.94 | 29.4 |
| Dog | 10 (mg/kg) | 2.93 (1.5) ^c | 1.7 (0.6) | 5.1 (1.4) | 37.7 (13.2) | 92.3 (32.2) |
| | 80 (mg/kg) | 7.4 (6.7-8) | 4-30 | - | 215 (147-283) | |
| Monkey | 10 (mg/kg) | 0.92 | 12 | 6.6 | 13.9 | 80 |
| Man | 5 ^d mg | 0.04 (.01) | 1.5 (0.56) | 6.5 (2.0) | 0.37 (0.11) | 80.4 (11) |
| | 38 ^e mg | 0.31 (0.1) | 1.7 (0.5) | 5.9 (1.3) | 2.45 (1.13) | - |
| | 200 ^f mg | 0.92 (0.08) | 2-4 | 17.3 (3.5) | 12.9 (1.12) | - |
| | 400 ^f mg | 2.05 (0.2) | 4-6 | 13.4 (0.7) | 31.5 (1.67) | - |

^a -AUC values are extrapolated to infinite time.

^b - F is the oral bioavailability corrected following intravenous administration.

^c - Numbers in parenthesis is standard deviation.

^d - Data represent mean values following three treatments (1 x 5 mg tablet, 5 x 1 mg tablet, and 5 x 1 mg capsule).

^e - Six volunteers were given one capsule contained 38 mg of finasteride.

^f - Five volunteers were given a single dose of 200 or 400 mg of finasteride.

Finasteride is quickly and well absorbed in dogs (95%), monkeys (81%), and man (80%) but poorly in the rat (29-61%). In humans, absorption reaches a maxima approximately 2 hours following a 1, 5, or 38 mg dose. Once absorbed, finasteride is widely distributed. Rats dosed with a 5 mg/kg iv dose had radioactivity in the liver, fat pads, Harders gland, adrenals, intestines, epididymes, prostate, seminal vesicles, kidneys, testes, and heart. Following 21 daily dosings, radioactivity increased 61 fold in fat tissue compared to a single administration. However, the increase was still only a fraction of the plasma drug concentration. AUC values also increased in all species examined following multiple administrations (Table 2) compared to single administrations. However, human AUC values after 17 days of treatment are much greater than rat AUC values obtained after administration of 80 mg/kg/day for one year.

Table 2. AUC values obtained for rat, mouse, dog, rabbit, and humans following multiple oral administrations.

| Study Number | Species/Sex | Drug Week | Oral Dose (mg/kg/day) | Mean AUC value (ug*hr/ml) | Human Male Equivalent ^a |
|------------------|------------------|-----------|-----------------------|---------------------------|------------------------------------|
| TT #86-058-0 | Rat (male) | 52 | 20 | 11.94 | 239 |
| | Rat (male) | 52 | 40 | 15.44 | 308 |
| TT #87-114-0 | Rat (male) | 14 | 80 | 24.42 | 488 |
| | Rat (male) | 14 | 160 | 44.31 | 886 |
| | Rat (female) | 14 | 320 | 109.51 | 2190 |
| TT #87-016-0, -1 | Mouse (male) | 13 | 250 | 91.01 | 1820 |
| TT #87-057-0 | Dog (male) | 52 | 45 | 140.48 | 2805 |
| TT #87-704-0 | Rabbit (male) | 11 | 80 | 217.20 | 4344 |
| TT #94-9014 | Macaque (female) | 14 | 2 | 1.34 | 26.8 |
| | Man | 17 | 5 mg/day | 0.4 | - |
| | Man | 17 | 1 mg/day | 0.05 | 1 |

^a-Approximate multiples of human exposure were based on calculated AUC (0-24 hr) values for animals and mean AUC (0-24 hr) value in men receiving the recommended dose of 1 mg/day for 17 days (AUC=0.05 ug*hr/ml).

The metabolism of finasteride is quantitatively similar in all species. Finasteride is converted to ω -hydroxyfinasteride and then finasteride- ω -oic acid. The formation of these two metabolites has also been reported in vitro with human cytochrome P450 isozyme CYP3A4. Other metabolites (6 α OH finasteride and ring-OH finasteride) have been observed in animals. These latter metabolites were observed in the urine and feces while the previous metabolites were reported in plasma. The major metabolite in all species is the ω -hydroxyfinasteride compound and accounts for 33% of radioactivity. The finasteride ω -oic acid metabolite represents 1-18% of radioactivity. All the metabolites have 10-20% of the enzyme inhibitory activity of the parent compound.

Following oral administration of finasteride, the majority of the radioactivity is excreted in the feces for all species. In dogs given an 80 mg/kg dose, less than 6% of the radioactive dose was excreted in urine. Additionally, 53-77% of the radioactivity excreted in the feces was parent compound, in contrast to that observed at a lower dose (10 mg/kg), which was eliminated mainly as metabolites. In humans given a dose of 38 mg, fecal and urine excretion was 57% and 39%, respectively. Less than 1% of the radioactivity in either the urine or feces was parent compound.

On June 2, 1997, the Sponsor was asked to submit and cite studies where the nonclinical AUC values were obtained from in order to calculate human equivalents in the proposed label. The Sponsor was able to submit the information contained in Table 2. Table 2 represents the AUC values (based on 0-24 hour AUC) calculated for the male rat, female rat, male mouse, male dog, and male rabbit. The human AUC_{0-24 hr} value used (0.05 ug*hr/ml) for all comparisons was obtained following oral administration of 1 mg/day. The AUC values listed in Table 3 will be used for evaluating the potential risk of finasteride to humans. [Reviewer's Note: The AUC values represented in Table 2 differ from the values noted in the pharmacology reviews for Proscar (NDA 20-180). The AUC values in Table 2 are identical to those values submit by the Sponsor in order to calculate human multiples during the review of NDA 20-180 (submitted by fax on April 9, 1992). In a telephone discussion with the reviewing pharmacologist of NDA 20-180, the AUC values in the pharmacology reviews are apparently values obtained at different time periods (e.g., 0-6 hours vs. 0-24 hours).]

Single Dose Toxicity Studies -

In summary, the acute toxicity of finasteride was evaluated in mice and rats. LD₅₀ values were determined after a oral, intraperitoneal, or subcutaneous administration. These values ranged from 373 mg/kg to greater than 2 g/kg in mice and rats. In dogs, only two doses of finasteride (500 and 1000 mg/kg) were given. Emesis was only observed at the higher dose.

Repeated-Dose Toxicity Studies-

The potential subchronic and chronic (up to one year) toxicity of finasteride was determined after intravenous, subcutaneous, and oral administrations. The one-year toxicity studies were all oral administrations. Since finasteride is a highly specific inhibitor of 5 α -reductase, dose-dependent, pharmacologically-mediated finasteride findings were reported. The oral administration of finasteride at doses of ≥ 1 mg/kg/day produced significant reductions (>70%) in serum and prostatic dihydrotestosterone (DHT). A no-effect dose in rats for conversion of testosterone to DHT was 100 ng/kg/day (approximately 0.001 times the human exposure: all comparisons are obtained from AUC values given in Table 3) after 4 days of treatment. Prostate, seminal vesicles, liver, adrenal, thyroid, testis, epididymis, and uterus are target organs in the rat while liver and prostate are target tissues in dogs. Rats treated with 40 mg/kg/day (270 times the human exposure) or greater for greater than 6 months displayed an increased incidence of focal Leydig cell hyperplasia. Prostate weights decreased 36-72% in both rats and dogs treated with doses of ≥ 20 mg/kg/day (240 times the human exposure) and ≥ 5 mg/kg/day (approximately 310 times the human exposure) for 1 year, respectively. Seminal vesicle weights also decreased (79%) in rats following administration of 80 mg/kg/day finasteride (480 times the human exposure) for 31 weeks. Uterine weights decreased 18-40% in rats regardless of dose (5-800 mg/kg/day) and duration (3, 6, or 12 months). Both rats and dogs had increased liver weights when given doses greater than 20 and 15 mg/kg/day (approximately 930 times the human exposure) for 1 year, respectively. Increased liver enzymes (ALP, AST, AST) were observed in some dogs from the high dose group. P-450 induction was also observed in both rats and dogs treated with 80 mg/kg/day and 45 mg/kg/day (2800 times the human exposure), respectively. However, no histopathologic

changes were noted in the liver of either species. Histopathologic findings in rats included prostate atrophy, adrenal cortical vacuolation, thyroid follicular cyst, focal hyperplasia in testes, small/flattened seminal vesicles, discoloration with epithelial vacuolization in epididymes, and atrophy of the thymus. Histopathologic findings in dogs also included atrophy of the prostate and thymus, and liver hepatocyte vacuolation in animals given 80 mg/kg/day for 14 weeks (approximately 5600 times the human exposure). Atrophy of the prostate was the only finding with a 1 year treatment of 45 mg/kg/day (2800 times the human exposure) in dogs.

Carcinogenicity Studies

The carcinogenic potential of finasteride was evaluated in mice and rats. Finasteride was administered at doses of 2.5, 25, and 250 mg/kg/day (18, 180, and 1820 times the human exposure, respectively) for 83 weeks to mice. The study was terminated at this period due to the high mortality in the high dose group (56%). An increased incidence of Leydig cell adenomas of the testes was observed in the high dose males (16 of 50 animals). Leydig cell hyperplasia and elevated serum LH were observed in male mice of the mid and high dose groups. The degree of Leydig cell hyperplasia is correlated with LH levels. This hypothesis was supported in an ancillary pharmacology study in which the administration of exogenous DHT to rats treated with finasteride (250 mg/kg/day) prevented the occurrence of 10-fold elevations in plasma LH levels and Leydig cell hyperplasia. The NOEL for Leydig cell changes in the mouse carcinogenicity study was 2.5 mg/kg/day (approximately 18 times the human exposure). In the rat, administration of 160 mg/kg/day (890 times the human exposure) to male rats and 320 mg/kg/day (2190 times the human exposure) to female rats did not increase the incidence of any tumor type after 2 years of treatment. The survival of these animals was around 18-26% for control groups and 16-42% for treatment groups. Body weights in mid and high dose female groups were increased (18% and 14%, respectively) while body weights in high dose male animals were decreased (13%). At necropsy, small prostate and seminal vesicles were observed in all treated male animals (not dose-related).

Reproductive Toxicity Studies

Several reproductive toxicity studies have evaluated the potential of finasteride to cause developmental or fetal toxicity. Finasteride was administered orally to rabbits, rats, and monkeys. Five segment I studies were performed using male immature and mature rats, one segment I study with female rats, and one study used male rabbits. No effect on fertility, sperm count, or ejaculate volume were observed in rabbits treated with 80 mg/kg/day (4,300 times the human exposure) for 12 weeks. In the male rat fertility studies, doses of 20, 40, and 80 mg/kg (240, 310, and 480 times the human exposure, respectively) were given for 12 to 31 weeks. Additionally, lower doses of 0.1, 1, or 3 mg/kg/day (approximately 0.8, 8, and 20 times the human exposure) were also administered to male rats for 260 days. In summary, decreases in fertility and fecundity were reported in male rats treated with 1 mg/kg/day (approximately 8 times the human exposure) or greater. No other effects on fertility parameters were observed. The decreases in fertility were due to decreased seminal secretions and copulatory plug formations as a result of the decrease in prostate and seminal vesicle

weights. These organ weights were decreased in all treated animals. Histopathologic examinations revealed vacuolization of epithelial cells in the epididymal head in male rats treated with 1 mg/kg/day for 260 days or 80 mg/kg/day for 31 weeks. Other histological findings included atrophy of the prostate and seminal vesicles, and Leydig cell hyperplasia in rats treated with 80 mg/kg/day for 31 weeks. No histological changes were noted in the testes or prostate of animals treated with 3 mg/kg/day for 260 days. A six week recovery period following 12 or 30 weeks of drug treatment restored fertility and fecundity indices to control values. However, Leydig cell hyperplasia and epididymal vacuolization were still present following the recovery phase.

In the female segment I fertility study, dose-related decreases in male and female fetal weights were observed following the administration of 0.1, 3, or 100 mg/kg/day for 2 weeks prior to mating, 16 days during mating, and 20 days of gestation. Additionally, decreased anogenital distance was observed in male fetuses at all dose levels (approximately 0.7, 20, and 670 times the human exposure). A 20% body weight decrease was noted in the high dose group.

In segment II reproductive toxicity studies, oral administration of 0.003 mg/kg/day (approximately 0.02 times the human exposure) or greater to pregnant Sprague Dawley rats (days 6-20 of gestation) resulted in decreases of anogenital distances. The critical period for the reproductive effects is on gestational days 14-19. Hypospadias were also reported in 16/124 male pups from rats treated with 0.1 mg/kg/day (approximately 0.7 times the human exposure) or greater. Transient nipple development was observed in male fetuses from rats treated with 0.03 mg/kg/day (approximately 0.2 times the human exposure) or greater. Additionally reproductive effects included dose-related decreases in pup weight, litter size, postimplantation, perinatal or postnatal survival. Segment II studies were also conducted with New Zealand white rabbits. Administration of finasteride (10 mg/kg/day; approximately 540 times the human exposure) to pregnant rabbits (gestation day 6-17) increased preimplantation losses, number of resorptions, and dead fetuses.

Late gestational or developmental toxicities were evaluated in Sprague Dawley rats. As previously noted, anogenital distance and transient nipple development were observed in male fetuses of dams given 0.03 mg/kg/day or greater during gestation day 15 to day 21 of lactation. Developmental effects were not reported in any treatment group. Reproductive performance of F1 females was not affected by in utero drug treatment. Male fetuses from dams treated with 3 mg/kg/day (approximately 20 times the human exposure) displayed significantly decreased mating and fertility.

More recently, the reproductive toxicity potential of finasteride was evaluated in pregnant Rhesus monkeys. Animals (mean=6.5 kg; range= kg) were either treated intravenously with 8, 80, or 800 ng/monkey/day or orally with a dose of 2 mg/kg/day during day 20 to 100 of gestation. The treatment period encompassed the critical periods of embryonic and fetal development including that of external genital differentiation. Control groups were also included for each route of administration. No drug-related effects on physical signs or maternal body weight were reported in any treatment group. Additionally, no external genital abnormalities were observed in male or female fetuses of pregnant monkeys intravenously treated with up to 800 ng/day (123 ng/kg/day or 0.16 ng/cm²/day). Similarly,

no abnormalities were noted in female fetuses of pregnant monkeys orally treated with 2 mg/kg/day of finasteride (27 times the human exposure). However, external genital abnormalities (hypospadias; 83%: preputial adhesions to the glans; 100%: underdeveloped scrotum; 100%: small penis; 83%: and prominent midline raphe; 100%) were observed in male fetuses of pregnant monkeys orally given 2 mg/kg/day of finasteride. Changes in fetal anogenital distances or prostatic and seminal vesicular weights were not reported in any fetus.

Mutagenic Potential

The genotoxic potential of finasteride was evaluated in microbial and mammalian mutagenesis assay, in vitro alkaline dilution assay, in vivo chromosome aberration assay (TT #88-8600 and TT #88-8601), and in vitro chromosome aberration assay. No genotoxicity was noted in these assays, except for the in vitro chromosome aberration assay. An increase incidence of chromosome aberrations were reported in Chinese hamster ovary cells treated using high concentrations of finasteride (300-500 uM).

Comments:

The pharmacology of finasteride has been examined and well characterized. Oral administration of finasteride at doses ≥ 1 mg/kg/day produces significant reductions ($> 70\%$) in serum and prostatic DHT in monkeys, dogs, rats, and humans. The decreased DHT results in reductions in prostatic size in rats, dogs, and men; and increases in hair growth in the stump-tail macaque. This compound is a specific inhibitor of 5α -reductase, the enzyme which converts testosterone to dihydrotestosterone. Of the two isozymes of 5α R found in rats, monkeys, and humans, the monkey 5α R isoforms have a greater homology and similar distribution to human 5α R. Additionally, finasteride selectively inhibits human and monkey type 2 5α R while inhibition of the rat and dog isoforms is not greatly differentiated. Thus, any biological activity observed in the rat and dog studies are due to the inhibition of both isozymes of 5α R.

The preclinical toxicology studies conducted with finasteride demonstrated a low order of toxicity and many of the changes observed in the studies were related to the pharmacological properties of the drug. For example, the drug prevents DHT-mediated differentiation of male external genitalia and accessory sex glands in the rat at very low concentrations. In rats, the lowest oral dose which caused a reproductive effect (decreased anogenital distance) was 0.003 mg/kg/day (approximately 0.02 times the human exposure). External genitalia of male fetuses (hypospadias) were also affected when dams were given a dose of 0.1 mg/kg/day (approximately 0.7 times the human exposure). In contrast, an intravenous dose of 800 ng/monkey had no drug-related reproductive effects in treated monkeys while an oral dose of 2 mg/kg/day caused external genital abnormalities (i.e., hypospadias). The 100 fold difference (on a mg/kg basis) in teratogenicity between the rat and monkey may be the result of the specificity of finasteride on the 5α R. Since finasteride is not a selective inhibitor of rat 5α R, a lower dose will cause a greater decrease in DHT when compared to monkey. Thus, the greater effect to rat male fetuses.

Other findings are reported in animals following the chronic exposure to finasteride. In the rat, these include prostate atrophy, adrenal cortical vacuolation, thyroid follicular cyst,

focal hyperplasia (Leydig cell) in testes, small/flattened seminal vesicles, discoloration with epithelial vacuolization in epididymes, and atrophy of the thymus. These findings could be observed within four days of treatment, depending on the dose. The infertility reported in the segment I reproductive toxicity studies was attributed to these findings. In rats, a seminal plug is necessary for pregnancy to occur. Since these accessory sex organs are DHT dependent, plugs could not be formed in the dams after male rats had been treated with 80 mg/kg/day up to 24 or 31 weeks. In rabbits, no decreases in fertility or fecundity were reported.

The target organs in dogs were the liver (hepatocyte vacuolation), prostate, and thymus (atrophy of the prostate and thymus) following a dose of 80 mg/kg/day for 14 weeks. Atrophy of the prostate was the only finding with a 1 year treatment of 45 mg/kg/day finasteride in dogs (Leydig cell hyperplasia was not observed). The apparent lower toxicity of finasteride in dogs may also be related to the specificity of the finasteride for the $5\alpha R$ isozymes. In dogs, the IC_{50} ranged in the μM ranges (μM) while the range was in the nM range (nM) in rats.

In the carcinogenicity studies, Leydig cell adenomas were observed in mice after 19 months of treatment with 250 mg/kg/day (1800 times the human exposure). In rats, no type of lesion was observed. However, Leydig cell hyperplasia was observed in rodents (mice and rats) and dogs. The increase in Leydig cell changes was associated with a 200-300% increase in serum LH levels. Administration of exogenous DHT to rats treated with high doses of finasteride (250 mg/kg/day) for 14 weeks prevented elevation of serum LH levels and consequent Leydig cell hyperplasia. In men, only a slight (10%), nonsignificant increase in serum LH levels has been observed following chronic finasteride administration which may be the result of a lower dose.

Since the product is only intended for men, women would only be exposed via semen. The sponsor has previously suggested that the finasteride levels in semen are too low to affect DHT levels in women if they were to be exposed to finasteride via the semen. In males, a dose of 1 mg/day will result in finasteride levels in semen 650 times below the dose required to decrease male systemic levels of DHT. However, the same information is not available in women.

The highest semen concentration of finasteride measured was 1.5 ng/ml following 17 daily oral administrations of 1 mg finasteride. Therefore, the maximum potential exposure to a pregnant woman (50 kg) through semen would be 8 ng, based on a 5 ml ejaculate volume. Assuming a complete absorption of finasteride from the vagina, daily exposure to semen, a 5-ml ejaculate, and a body weight of 50 kg, the Sponsor estimated on a body weight comparison that the maximum exposure is at least 750 times lower than the dose at which no adverse effect was observed in fetuses of pregnant Rhesus monkeys given finasteride intravenously (0.16 ng/kg for women vs. 120 ng/kg/day for monkeys).

A much lower safety margin is calculated if a body surface area comparison is used instead of a body weight comparison. Assuming a surface area of 5000 cm^2 for monkeys and 16000 cm^2 for women, the safety margin is 320 times instead of 750 times [0.16 ng/ cm^2 /day for monkeys vs. 0.0005 ng/ cm^2 /day for women]. [Reviewer's Note: Since the levels of finasteride which affect a women's DHT levels has not been determined, a surface body area equivalent is being used to make extrapolations to potential women exposure.] Although a

lower safety margin is obtained with a body surface area comparison, a larger margin of safety may exist if a no-adverse-effect-level (NOEL) is determined by the Sponsor. A higher intravenous or lower oral dose could have been administered to establish the NOEL. The Sponsor may want to repeat a macaque teratogenicity study with lower oral doses in order to provide the oral NOEL dose. The oral route is more preferable since oral administration is the clinical route.

In pregnant macaque monkeys, a dose of 2 mg/kg/day during gestation resulted in a teratogenic effect at a dose which corresponds to 27 times the human male exposure (based on AUC values). Currently, the highest non-teratogenic dose is an intravenous administration of 800 ng/day (123 ng/kg/day or 0.16 ng/cm²/day), which corresponds to 320 times the estimated human female exposure via semen. Since the female comparison is more critical, studies are needed to establish the AUC values of finasteride in women and the dose at which finasteride decreases DHT levels. The pharmacokinetic response to finasteride by women may differ from males. By understanding the pharmacokinetic profile of finasteride in women, a more accurate safety margin can be established. If a large safety margin is observed with the new data, this may result in a change in the pregnancy category.

In terms of the pregnancy category, the content and format for labeling of human prescription drugs is described in the Federal Register (44:37464-37465). Under the heading of teratogenic effects, the labeling is required to identify one of the following categories that applies to the drug: Pregnancy Category A, B, C, D, and X. The most appropriate label for finasteride is Category X. "If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit, the labeling shall state: Pregnancy Category X." In addition, no reference is made in these passages to the concentration of drug that does or does not produce the fetal abnormalities. Thus, the findings described above clearly indicate that the labeling for finasteride be designated as "Pregnancy Category X".

In summary, the non-clinical data provided are adequate to support the approval of finasteride for the proposed use. Teratogenic effects are observed in rats at doses significantly below intended human exposure. More importantly, only a 27 fold difference exists between the AUC value where teratogenicity is observed in the macaque monkey, a more relevant species compared to rats, and the AUC values observed in human males. Thus, this product is contraindicated in women of childbearing potential and the pregnancy category is X. The other findings observed occurred either at exposure significantly higher than those achieved with expected human exposures (i.e., decreased prostate weights, increased liver weights) or were primarily rodent-specific (i.e., decreased fertility). The Leydig cell hyperplasia/adenoma observed in the non-clinical studies were the result of the increased sera LH levels. LH increases were not observed in humans, but the lack of serum LH increase may be the result of lower dose administrations compared to the non-clinical toxicity studies.

Conclusion: From a pharmacological standpoint, approval is recommended for this NDA.

Recommendations:

1. The Sponsor is encouraged to identify the oral no-observable-effect-level for the teratogenicity of finasteride in pregnant macaque monkeys.
2. The Sponsor is encouraged to identify the female no-observable-effect-level for changes in serum DHT levels following oral administration of finasteride.

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