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From: Silber, Cynthia
Sent: Thur 6/4/2009 11:50:35 AM
Importance: Normal
Subject: Updated: Propecia RMP update discussion
RMST MK0906 Agenda 04Jun2009.doc
PROPECIA RMP Final.pdf





MK-0906

**Risk Management Safety Team
Meeting**

Date: 04 June 2009

Time: 11:00 AM-12:00 PM

Location: T/C 1-877-423-2663 PIN#
414467

Core Team members: Ahn, Siyoung; Dandora, Reetu; Hormbrey, Janet Mary; Kaufman, Keith D.; Koch, Gregory; Levine, Jeffrey; Majekodunmi, Kolade; Merritt, Charlotte; Prahalada, Srinivasa; Preuveneers, Geert; Rhodes, Thomas; Round, Elizabeth M.; Visser, Hester; Alberts, Christine M.; Silber, Cynthia G.

Agenda

I. Discussion of Update of Propecia Risk Management Plan

Core Team (60 min)

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

1

TABLE OF CONTENTS

	<u>PAGE</u>
List of Tables	3
PART I	6
1. Safety Specification	6
1.1 Nonclinical	6
1.1.1 Nonclinical Safety Concerns	6
1.1.2 Special Population Use—Additional Nonclinical Data Needs	7
1.2 Limitations of the Human Safety Database	7
1.2.1 Exposure	7
1.3 Populations Not Studied in the Pre-approval/authorisation Phase	12
1.4 Postmarketing (Nonstudy) Experience	15
1.4.1 Projected Postmarketing Usage Data	15
1.4.2 Actual Postmarketing Usage Data	15
1.4.3 Regulatory Action Taken	15
1.5 Adverse Reactions	15
1.5.1 Newly Identified Important Safety Concerns	15
1.5.2 Details of Important Identified and Important Potential Risks	15
1.6 Identified and Potential Interactions With Other Medicinal Products, Food, and Other Substances	41
1.7 Epidemiology of the Indication(s) and Important Adverse Reactions	41
1.7.1 Incidence, Prevalence, Mortality, and Demographic Profile of the Target Population	41
1.7.2 Important Co-Morbidity in the Target Population	42
1.7.3 Epidemiology of the Condition in the Target Population when Unexposed to the Product	42
1.8 Pharmacological Class Effects	48
1.9 Additional Requirements	50
1.9.1 Potential for Overdose	50
1.9.2 Potential for Transmission of Infectious Agents	51
1.9.3 Potential for Misuse for Illegal Purposes	52
1.9.4 Potential for Off-Label Use	52
1.9.5 Potential for Off-Label-Pediatric Use	54
1.10 Summary—Ongoing Safety Concerns	55
2. Pharmacovigilance Plan	55
2.1 Routine Pharmacovigilance Practices	55
2.2 Summary of Safety Concern and Planned Pharmacovigilance Actions	55
2.3 Detailed Action Plan for Specific Safety Concerns	56
2.4 Overview of Study Protocols for the Pharmacovigilance Plan	58
2.5 Risk Management Plan Updates	58
2.6 Summary of Outstanding Actions, Including Milestones	58

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

2

TABLE OF CONTENTS (CONT.)

	<u>PAGE</u>
PART II	59
3. Evaluation of the Need for a Risk Minimization Plan	59
3.1 Summary Table for Important Safety Concerns	59
3.2 Potential for Medication Errors	64
4. Risk Minimization Plan	66
5. Summary of the Risk Management Plan	67
6. Contact Person for this RMP – Provided as a separate component.	67
7. List of References	68

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

3

List of Tables

	<u>PAGE</u>
Table 1 Exposure to Finasteride by Duration	7
Table 2 Exposure to Finasteride by Dose	8
Table 3 Exposure to Finasteride by Age and Gender	8
Table 4 Exposure to Finasteride by Ethnic Origin	8
Table 5 Exposure to Finasteride by Country	9
Table 6 Finasteride 1 mg (PROPECIA) Global Patient Exposure Estimate ex-Japan As of September 30, 2008	10
Table 7 Finasteride 1 mg (PROPECIA) Patient Exposure Estimate by Region & Country As of September 30, 2008	11
Table 8 Finasteride 1 mg (PROPECIA) Patient Exposure Estimate by Age Group	11
Table 9 Drug-related Adverse Events for PROPECIA 1 mg in Year 1 Phase III Controlled Studies (087,089 and 092) Incidence \geq 1%	49
Table 10 Adverse Reactions Reported in \geq 1% of Subjects Over a 24-Month Period and More Frequently in the Group Receiving AVODART™ Than the Placebo Group (Randomized, Double-Blind, Placebo-Controlled Studies Pooled) by Time of Onset	50
Table 11 Off-Label Use in Men and Gender Not Specified Populations Twenty Most Frequent Reported ADRs	53
Table 12 Off-Label Use in Men and Gender Not Specified Populations Most Frequent Serious ADRs	54
Table 13 Pediatric Medication Error: 20 Most Frequent ADRs	66

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

4

Product Details

Invented name of the medicinal product (product short name)	PROPECIA and related medicinal products: Capipro, Finasterid, Folitabs, Growancer and Pervil
Active substance(s) (INN or common name)	Finasteride
Pharmaco-therapeutic group (ATC Code)	5-alpha-reductase inhibitor (D11AX10)
Medicinal product code (from Eudravigilance)	Medicinal product code ranges for PROPECIA PRD108833 to PRD108857 Medicinal product codes for related medicinal products: PRD108860 (Folitabs, Spain) PRD108859 (Capipro, Sweden) PRD108858 (Finasterid, Germany) PRD108871 (Pervil, Greece) PRD108870 (Growancer, Portugal)
Authorization procedure(s) (centralized, mutual recognition, decentralized, national)	Mutual recognition
Name of marketing authorization holder or applicant	Merck Sharp & Dohme GmbH Austria Merck Sharp & Dohme B.V. Denmark Merck Sharp & Dohme B.V. Finland Laboratoires Merck Sharp & Dohme – Chibret France Merck Sharp & Dohme GmbH Germany MSD/Vianex S.A. Greece Merck Sharp & Dohme B.V. Iceland Merck Sharp & Dohme (Italy) S.p.A. Italy Merck Sharp & Dohme B.V. Luxembourg Merck Sharp & Dohme B.V. The Netherlands Merck Sharp & Dohme Lda. MAH for Growancer: Fontelabor - Produtos Farmacêuticos, Sociedade Unipessoal, Lda Portugal Merck Sharp & Dohme de Espana, S.A. Spain Merck Sharp & Dohme B.V. Sweden
Date and country of first authorization worldwide	Not applicable
Date and country of first launch worldwide	Not applicable
Date and country of first authorization in the EEA	17 April 1998 / Sweden
Date and country of first launch in the EEA	17 April 1998 / Sweden

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

5

Brief description of product (chemical class, mode of action, etc.)	4-azasteroid, which inhibits human type two 5-reductase (present within the hair follicles) with greater than 100-fold selectivity over human type one 5-reductase, and blocks the peripheral conversion of testosterone to the androgen dihydrotestosterone (DHT).		
Indication(s)	Early stages of androgenetic alopecia in men. PROPECIA stabilizes the process of androgenetic alopecia in men 18-41 years of age. Efficacy in bitemporal recession and end-stage hair loss has not been established.		
Dosage	1 tablet (1 mg) daily with or without food.		
Pharmaceutical form(s) and strength(s)	Film-coated tablets		
Data lock point for RMP	18-Aug-2008	Version	1.0

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11-Feb-2009

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

6

PART I

1. Safety Specification

1.1 Nonclinical

1.1.1 Nonclinical Safety Concerns

SAFETY CONCERN (from non clinical studies)	RELEVANCE TO HUMAN USAGE
<p>Exposure During Pregnancy in Animals Potential developmental effects of finasteride were evaluated in 3 species (rat, monkey and rabbit). The oral dosage studied ranged from 5 to 5000 times the recommended human dose of 1 mg/kg. Oral administration of finasteride to pregnant rats and monkeys during the period of male external genital differentiation resulted in hypospadias, an expected pharmacological effect of the drug [642; 641; 646]. There were no other abnormalities in either male or female offsprings of all 3 species studied.</p> <p>Studies in the rhesus monkey confirmed that exposure of pregnant women to finasteride in semen is not considered a risk to the developing male fetus. In rhesus monkeys, treatment with oral doses of 2 mg/kg/day has also resulted in external genital abnormalities. Intravenous doses of up to 800 ng/day in rhesus monkeys have not shown any effects in male fetuses. This represents at least 750 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day [646].</p>	<p>These findings may have human relevance for females; therefore, PROPECIA™ is contraindicated for use in women in the EUSPC, and is contraindicated for use in women who are or may be pregnant in all markets. The observation in rats and monkeys is not relevant to the intended male patient population.</p>
<p>Male Fertility Studies in Animals Oral administration of finasteride resulted in decreased fertility in male rats. Detailed studies have shown that the decreased fertility in rats is species specific and is related to decreased prostatic and seminal vesicular secretion (an expected pharmacological effect in rats), leading to decreased vaginal seminal plug formation. In rats, formation of vaginal seminal plug immediately following mating is critical for sperm transport into the uterus [726; 551]. In these studies, finasteride had no effect on fertilizing capacity of the rat sperm, when the sperm was directly deposited into rat uterus [551]. Furthermore, finasteride had no effect on fertility in male rabbits. Finasteride had no effect on spermatogenesis in any of the species (rat, mouse, dog) studied.</p>	<p>The effect of finasteride on vaginal seminal plug formation and subsequent fertility in rats is species-specific, and not relevant for humans.</p>

1.1.2 Special Population Use—Additional Nonclinical Data Needs

No additional non-clinical studies have been conducted or are planned to support the use of finasteride in special populations.

Clinical**1.2 Limitations of the Human Safety Database****1.2.1 Exposure****Clinical Trial Exposure**

The clinical development program for finasteride for the treatment of androgenetic alopecia was initiated in January 1991 and includes the following studies of at least 4 weeks duration (P031, P047, P056, P065, P081, P087, P089, P092, P094, P099, P101, P104/P106, P111, P114, and P121) and their extensions (for P047, P081, P087, P089, P092, P099, and P101) in which patients were exposed to finasteride. Details of these studies can be found in Annex 3.

Across the studies identified above, approximately 3400 patients were exposed to finasteride. The mean duration of exposure to finasteride (≥ 1 mg) was 748.9 days, with a cumulative exposure of 6976 patient years.

Details of the exposure to finasteride by duration, dose (1 or 5 mg), age, gender, ethnic origin and country are shown below in Table 1 through Table 5. These tables do not include the exposure data from one clinical pharmacology study in which 12 subjects received finasteride 1 mg for 17 days. In addition, exposure data from a Phase IIb/III study conducted in Japan as part of the development program for finasteride in the treatment of androgenetic alopecia (278 patients exposed to finasteride 0.2 mg or 1 mg) are not included.

Table 1

Exposure to Finasteride
by Duration

Duration of exposure (Days)	Patients	Mean Number of Days Exposed	Patient Years
≤ 90	317	30.7	26.7
91-180	223	143.6	87.7
181-270	133	216.3	78.8
271-360	611	333.3	557.9
361-720	622	563.8	960.8
721-10180	550	825.6	1244.1
10181-1440	316	1316.1	1139.4
1441-1080	602	1654.8	2729.3
1081-2240	24	2108.4	138.6
>2240	2	2301.5	12.6
≤ 90 to >2240	3400	748.9	6976.1

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

8

Table 2

Exposure to Finasteride
by Dose

Finasteride	Patients	Mean Number of Days Exposed	Patient Years
Any Dose (1 or 5 mg)	3400	748.9	6976.1
1 mg	3210	772.0	6789.4
5 mg	304	224.1	186.6

Table 3

Exposure to Finasteride
by Age and Gender

Age Group	Patients		Mean Number of Days Exposed		Patient Years	
	M	F	M	F	M	F
< 65	3333	67	753.8	504.9	6883.3	92.7
≥ 65	0	0	0	0	0	0

Table 4

Exposure to Finasteride
by Ethnic Origin

Ethnic Origin	Patients	Mean Number of Days Exposed	Patient Years
White	3068	753.5	6333.5
Black	140	614.6	235.7
Hispanic	112	759.3	233.0
Asian	62	738.0	125.4
Other	18	971.2	47.9

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

9

Table 5
Exposure to Finasteride by Country

Country	Patients	Mean Number of Days Exposed	Patient Years
Austria	49	841.4	113.0
Belgium	41	827.1	92.9
Brazil	24	791.6	52.0
Canada	92	1030.6	259.8
France	20	1186.8	65.0
Germany	13	579.2	20.6
Israel	17	982.8	49.3
Italy	19	297.5	15.5
Mexico	18	1062.7	52.4
Netherlands	51	1036.6	144.8
New Zealand	28	1020.2	78.3
Norway	26	1061.3	75.6
South Africa	103	1201.6	339.1
Spain	67	787.6	144.6
Switzerland	38	1097.5	114.3
United Kingdom	13	752.5	26.8
United States	2781	700.3	5335.7

Epidemiological Study Exposure

No epidemiological studies were performed.

Postmarketing (non study) Exposure

From widespread market launch in 1998, through September 30, 2008, approximately 1.83 billion tablets of finasteride 1 mg (PROPECIA) have been distributed worldwide excluding Japan. This translates to an estimated 4.6 million patients who have received finasteride 1 mg (PROPECIA) since launch (Table 6). This estimate assumes that each patient received a single dose of finasteride 1 mg (PROPECIA) per day for the treatment of male pattern hair loss, as recommended in the product label (EUSPC). It also assumes an annual attrition rate of 50%, which is consistent with known compliance rates for finasteride 1 mg, as well as for other prescription products. Within the 5 European member states of France, Germany, Italy, Spain, and the United Kingdom approximately 435 million tablets have been distributed, translating to an estimated 1.08 million patients in these countries who have received finasteride 1 mg (PROPECIA) since launch (Table 7).

Note: The primary data source of tablet sales is direct sales from the company to all distributors. These data do not account for wholesaler/pharmacy inventory that may not yet have reached patients. Therefore the data may slightly over-estimate patient usage data.

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

10

Table 6

Finasteride 1 mg (PROPECIA) Global Patient Exposure Estimate ex-Japan
As of September 30, 2008

Patients Remaining at Year End	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	YTD Sep 31, 2008	Estimated # of Patients since Launch
YE 98	93,561											93,561
YE 99	46,781	210,031										256,811
YE 00	23,390	105,015	223,182									351,587
YE 01	11,695	52,508	111,591	239,687								415,481
YE 02	5,848	26,254	55,795	119,843	243,794							451,534
YE 03	2,924	13,127	27,898	59,922	121,897	253,073						478,840
YE 04	1,462	6,563	13,949	29,961	60,948	126,536	262,548					501,968
YE 05	731	3,282	6,974	14,980	30,474	63,268	131,274	261,199				512,183
YE 06	365	1,641	3,487	7,490	15,237	31,634	65,637	130,599	265,645			521,736
YE 07	183	820	1,744	3,745	7,619	15,817	32,819	65,300	132,822	265,623		526,491
YE 08	91	410	872	1,873	3,809	7,909	16,409	32,650	66,411	132,812	192,992	
Total	187,031	419,651	445,491	477,501	483,778	498,237	508,687	489,748	464,878	398,435	192,992	4,566,430

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

11

Table 7

Finasteride 1 mg (PROPECIA) Patient Exposure Estimate by Region & Country
As of September 30, 2008

	Estimated Patient Exposure Since Launch	% of Global ex-Japan
Global Total ex-Japan	4,566,430	100%
Europe / CEE / MEA / Canada Total	1,541,172	34%
Germany*	363,665	8%
Spain*	257,012	6%
France*	207,314	5%
Italy*	194,689	4%
UK*	57,122	1%
US	2,107,367	46%
Asia Pacific	673,125	15%
Latin America	244,766	5%

* Included in Europe/CEE/MEA/Canada Total

The breakout of exposure across age groups and gender is not known; however, there is some *directional* data available from secondary market research sources which allows for rough estimates. Table 8 includes estimates of usage across age groups using data from the United States (US) and UK. In terms of usage across gender groups, data from the same US data it is estimated that approximately 95% of patients are males and 5% are females (similar data is not available for the UK or other markets).

Table 8

Finasteride 1 mg (PROPECIA) Patient Exposure Estimate by Age Group

Age Categories	Estimated % of Patient Usage by Age Group	
	US Data	UK Data
	Source: IMS, LRx Longitudinal Database (Jan-Dec 2007); Sample represents approximately 49% of all US prescriptions; Sample consists of approximately 95% men and 5% women	Source: IMS Mediplus Database (Jul 2007-Jun 2008); Sample taken from prescriptions generated by General Practitioners only; Sample consists of approximately 2,000 male patients
<18 yrs	0.5%	data not available
18-19 yrs	2%	3%
20-39 yrs	49%	74%
40-44 yrs*	1%	10%
45-49 yrs	data not available	data not available
≥50 yrs*	48%	13%

* Differences in usage estimates between the US and UK data sources for men ages 40 and older can be at least partially explained by the difference in the labeled indication. The USPC indication language sites the ages of men from the clinical studies in whom the safety and efficacy was demonstrated but does not limit usage to within that age range, whereas the EU label more specifically limits recommended use to men ages 18-41.

1.3 Populations Not Studied in the Pre-approval/authorisation Phase

In the overall clinical development program, the following populations have not been studied:

- Women of child-bearing potential.
- Children (patients less than 18 years of age) were excluded from the clinical trials.
- Elderly men (over 65 years of age) have not been studied with PROPECIA. However, significant safety data in this population exist from studies with PROSCAR™ (finasteride 5 mg).
- Patients with hair loss due to medical illness, alopecia areata, trichotillomania or any other form of pathological alopecia other than androgenetic alopecia.
- Patients with liver function tests at study entry 1.5 times above the upper limit of the normal range for AST and ALT.

With the exception of the exclusions regarding women and patients with hypersensitivity to any component of finasteride, the exclusion criteria applied in the Phase III controlled studies, were applied because the efficacy and safety data obtained from patients that met the exclusion criteria had the potential to confound the interpretation of the efficacy and safety data of PROPECIA when being studied as an investigational agent in the treatment of men with androgenetic alopecia.

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

13

Study Number	No. of Patients Exposed to This Product in the Study	Age Range*	Exclusion Criteria for Study
087 Phase III US Pivotal	471	18-41	<p>These exclusion criteria applied to the Phase III controlled studies (087, 089 & 092):</p> <p>1) A history of any illness or condition that, in the opinion of the investigator, might have confounded the results of the study or posed additional risk in administering finasteride to the patient, including multiple and/or severe allergies, or incompetency.</p> <p>2) A history of thyroid disease.</p> <p>3) Patients with liver function tests 1.2 times above the upper limit of the normal range (AST >26 mU/mL, ALT >30 mU/mL, total bilirubin >1.3 mg/dL).</p> <p>4) History or suspicion of any malignancy, excluding basal cell carcinoma of the skin.</p> <p>5) Patients whose sexual partner(s) was/were pregnant or planning pregnancy within the 12-month study period.**</p> <p>6) Patients who had had hair transplants, scalp reduction, or hair weaves.</p> <p>7) Patients with seborrheic dermatitis in the area of the scalp to be studied.</p> <p>8) Concurrent use of systemic corticosteroids, topical corticosteroids in the balding area studied or anabolic steroids.</p> <p>9) Use of the following drugs with antiandrogenic properties within 6 months of study entry: [Casodex™, (bicalutamide, Zeneca, UK)], flutamide, cyproterone acetate, topical estrogen, progesterone, cimetidine, spironolactone or ketoconazole (ketoconazole topical cream, [Nizoral™, Janssen, Titusville, NJ] is acceptable).</p> <p>10) Patients who had been treated with any of the following drugs within 1 year prior to entry: minoxidil (topical or oral), Accutane™ (isotretinoin, Roche Laboratories, Nutley, NJ), zidovudine, cyclosporine, diazoxide, phenytoin, systemic interferon, psoralens, streptomycin, penicillamine, tamoxifen, phenothiazines, or cytotoxic agents.</p> <p>11) History of treatment with any other investigational drug during the previous 3 months.</p> <p>12) History of treatment with finasteride or any other 5α-reductase inhibitor.</p> <p>13) Scalp hair loss due to medical illness.</p>
089 Phase III International Pivotal	308	18-41	
092 Phase III Frontal Hair Loss	166	20-41	

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

14

Study Number	No. of Patients Exposed to This Product in the Study	Age Range*	Exclusion Criteria for Study
			<p>alopecia areata, trichotillomania, or any other form of pathologic alopecia other than AGA.</p> <p>14) History of drug or alcohol abuse.</p> <p>These additional exclusion criteria applied to the Phase IV controlled studies (P114, and P121):</p> <p>15) Patients with liver function tests 1.5 times above the upper limit of the normal range (ULN) at screening (Medical Research Laboratories: AST >33 mU/mL, ALT >37.5 mU/mL, total bilirubin >1.6 mg/dL).</p> <p>16) Hypersensitivity to any component of finasteride.</p> <p>* Age range represents age at entry into study. Studies 087 and 089 were five-year studies; maximum age of exposed patients may have been as high as 46 years.</p> <p>** Exclusion 5 was not included in subsequent new and in second through fourth extension studies, after data from a study in pregnant rhesus monkeys demonstrated that the exposure of pregnant women to the small amount of finasteride in the semen of men taking finasteride 1 mg/day is not considered a risk for the developing fetus.</p>

The following populations have also been studied with similar exclusion criteria to those of the pivotal studies described above.

- Men 41-60 were studied in P121 (A 2-Year, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Tolerability of Finasteride 1 mg on Hair Loss in Men Aged 41 to 60 Years with Androgenetic Alopecia). A total of 286 men were exposed to finasteride 1 mg during the study with a mean duration of exposure of 623 days.
- Men with advanced hair loss were studied in a 2-year study P114 (A Double Blind, Placebo-Controlled, Multicenter Study to Determine the Effect of Finasteride in Men with Advanced Male Pattern Hair Loss). A total of 272 men were exposed to finasteride 1 mg during the study with a mean duration of exposure of 501.5 days.

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11-Feb-2009

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- Women (post-menopausal, ≤ 59 years of age) were studied in P101 (A 12-Month, Double-blind, Placebo-controlled Multicenter Study to Determine the Effect of Finasteride in Postmenopausal Women with Androgenetic Alopecia). A total of 67 postmenopausal women were exposed to finasteride 1 mg during the study with a mean duration of exposure of 343 days.

1.4 Postmarketing (Nonstudy) Experience

1.4.1 Projected Postmarketing Usage Data

Not applicable. The MAH does not anticipate any changes in usage.

1.4.2 Actual Postmarketing Usage Data

Actual exposure by age and gender is not known, however, general postmarketing usage estimates are presented in Section 1.2.1 Exposure.

1.4.3 Regulatory Action Taken

There have been no regulatory or manufacturer actions related to finasteride that resulted in marketing authorization withdrawal or suspension, failure to obtain marketing authorization renewal, restriction on distribution, clinical trial suspension, dosage modification, change in target population, or pharmaceutical changes for safety reasons.

1.5 Adverse Reactions

1.5.1 Newly Identified Important Safety Concerns

This is the initial RMP filing in the EU.

1.5.2 Details of Important Identified and Important Potential Risks

Two important identified risks (exposure during pregnancy, off-label use in women and adolescents) and 3 potential risks (persistent erectile dysfunction, male infertility, and depressive disorders) are discussed. For each risk, the data from the clinical trials are presented first followed by data from postmarketing use.

In the tables below, frequencies reported in number (%) of subjects experiencing the given adverse drug reaction (ADR) is based on the 1-year data from the Phase III controlled studies: 087 (U.S. Phase III Pivotal Study), 089 (International Phase III Pivotal Study) and 092 (Phase III Frontal Hair Loss Study) which were submitted in the Summary of Clinical Safety in the original marketing application. Across these 3 studies 945 patients were randomized to finasteride 1 mg and 934 patients were randomized to placebo.

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

16

Important Identified Risk	MedDRA Preferred Terms:															
Exposure during Pregnancy	Drug exposure during pregnancy															
Comment	Pregnant women should not take PROPECIA due to the potential risk of congenital anomalies in the external genitalia of the male fetus (i.e. hypospadias) during the period of development of the external male genitalia (8-14 weeks). The following section discusses clinical trial and postmarketing data related to pregnancy exposure, and includes presentation of all available data related to other pregnancy ADRs such as spontaneous abortion. Hypospadias data are presented in the postmarketing section; there were no reports of hypospadias in clinical trials.															
Seriousness/Outcomes	<p>At the start of the 1-year Phase III Pivotal studies (087 & 089) and the first extension studies, men whose sexual partner(s) was/were pregnant or planning pregnancy within the 12-month study period were excluded from the study. This exclusion was not included in subsequent new and extension studies when data from a study in pregnant rhesus monkeys demonstrated that the exposure of pregnant women to the small amount of finasteride in the semen of men taking finasteride 1 mg/day is not considered a risk for the developing fetus. (See Section 1.1.1 <u>Nonclinical Safety Concerns</u>.)</p> <p>During the 60 months of the Phase III Pivotal studies (1-year studies and four 1-year extensions) there were 54 reports of pregnancy in partners of men participating in the studies. Forty-eight of these were reported by finasteride-treated men and 6 by placebo-treated men. The incidence rate of pregnancy in the patient's sexual partner per 100 treatment years was somewhat higher for finasteride-treated men than for placebo-treated men (1.26 versus 0.71, respectively) with a rate ratio (finasteride to placebo) of 1.26:0.71 or 1.77.</p> <p style="text-align: center;">Number and Incidence Rate of Pregnancies Phase III Pivotal Studies</p> <table><tr><th rowspan="2">Treatment</th><th colspan="3">Phase III Pivotal Studies Combined</th></tr><tr><th>Number of Pregnancies in female partners of men taking finasteride</th><th>Treatment Years in male sexual partner</th><th>Incidence Rate (Per 100 Patient Years)</th></tr><tr><td>Finasteride</td><td>48</td><td>3,795</td><td>1.26</td></tr><tr><td>Placebo</td><td>6</td><td>849</td><td>0.71</td></tr></table> <p>Information on pregnancy outcome was available for 51/54 pregnancies and is summarized in the table below. There were no reports of congenital anomalies. The incidence rates for spontaneous abortion (12.2% and 16.7%, finasteride and placebo, respectively) and livebirths (87.8% and 83.3%, finasteride and placebo, respectively), determined using all known outcomes</p>	Treatment	Phase III Pivotal Studies Combined			Number of Pregnancies in female partners of men taking finasteride	Treatment Years in male sexual partner	Incidence Rate (Per 100 Patient Years)	Finasteride	48	3,795	1.26	Placebo	6	849	0.71
Treatment	Phase III Pivotal Studies Combined															
	Number of Pregnancies in female partners of men taking finasteride	Treatment Years in male sexual partner	Incidence Rate (Per 100 Patient Years)													
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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

17

Important Identified Risk	MedDRA Preferred Terms:																												
Exposure during Pregnancy	Drug exposure during pregnancy																												
	<p>except elective abortions as the denominator, were similar in the finasteride and placebo groups. Although the total number of pregnancies is small, there is no evidence to suggest that the incidence of spontaneous abortion in these reported pregnancies differs from that reported for the general population [976].</p> <p>Pregnancy Outcomes and Incidence of Outcomes Phase III Pivotal Studies</p> <table><tr><th rowspan="3">Outcome</th><th colspan="2">Number of Reports</th><th colspan="2">Phase III Studies Combined</th></tr><tr><th colspan="2">% of Reports</th><th colspan="2"></th></tr><tr><th>Placebo</th><th>Finasteride</th><th>Placebo</th><th>Finasteride</th></tr><tr><td>Elective Abortion</td><td>0</td><td>4</td><td>0[†]</td><td>8.9[†]</td></tr><tr><td>Spontaneous Abortion</td><td>1</td><td>5</td><td>16.7[‡]</td><td>12.2[‡]</td></tr><tr><td>Livebirths</td><td>5</td><td>36</td><td>83.3[‡]</td><td>87.8[‡]</td></tr></table> <p>[†] Percent of all outcomes. [‡] Percent of all outcomes excluding elective abortions.</p>	Outcome	Number of Reports		Phase III Studies Combined		% of Reports				Placebo	Finasteride	Placebo	Finasteride	Elective Abortion	0	4	0 [†]	8.9 [†]	Spontaneous Abortion	1	5	16.7 [‡]	12.2 [‡]	Livebirths	5	36	83.3 [‡]	87.8 [‡]
Outcome	Number of Reports		Phase III Studies Combined																										
	% of Reports																												
	Placebo	Finasteride	Placebo	Finasteride																									
Elective Abortion	0	4	0 [†]	8.9 [†]																									
Spontaneous Abortion	1	5	16.7 [‡]	12.2 [‡]																									
Livebirths	5	36	83.3 [‡]	87.8 [‡]																									
Severity and Nature of Risk	Not known																												
Frequency With 95% CI	Data not available																												
Background Incidence/Prevalence	Hypospadias occurs with a reported incidence ranging from 0.8-8 per 1000 live male births [569]. There is widespread variation in rates and temporal trends across time periods and countries. Greater detail is given in section 1.7.2 <u>Important Co-Morbidity in the Target Population</u>																												
Risk Groups or Risk Factors	Reproductive age women (due to potential for pregnancy)																												
Potential Mechanisms	Treatment of pregnant rats with finasteride results in feminization of the external genitalia of the male fetuses. This is a mechanism-based effect secondary to inhibition of 5 α -reductase Type 2. In humans, the urogenital folds fuse to form the penile urethra late in the first trimester, and the penile urethra is completely closed by the 14th week. Thus the potential for finasteride to have an impact on the external genitalia of a human male fetus is believed to be confined to gestational age of 8-14 weeks.																												
Preventability	Exposure to drug during pregnancy is preventable; therefore, the EUSPC and EUPPI labeling indicates that the medication is contraindicated in women.																												
Potential Public Health Impact of Safety Concern	Women should not take PROPECIA due to the potential risk of pregnancy exposure and congenital anomalies in the external genitalia of the male fetus (i.e. hypospadias) during the period of development of the external male genitalia (8-14 weeks). The expected public health impact is low, given the limited number of events relative to the usage of the product, although the potential impact to individual patients is substantial.																												

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

18

Important Identified Risk	MedDRA Preferred Terms:																																				
Exposure during Pregnancy	Drug exposure during pregnancy																																				
Evidence Source	Phase III Pivotal studies (087, 089) and their placebo-controlled extensions (087-10, 087-20, 087-30, 087-40, 089-10, 089-20, 089-30, and 089-40) WAES database																																				
Regulatory Action Taken	None																																				
Postmarketing Data	<p>The Worldwide Adverse Experience System (WAES) database was searched for spontaneous reports of exposure during pregnancy in patients treated with PROPECIA and in patients whose partners were treated with PROPECIA primary suspect therapy received from HCPs, including regulatory agencies, and consumers from market introduction (11-Sep-1997) through 18-Aug-2008. A total of 290 reports were identified.</p> <p>Reports are classified as prospective or retrospective. Prospective reports are those received before the outcome of the pregnancy is known, while retrospective reports are those received after the outcome of the pregnancy is known. A report is also classified as retrospective if an initial report is received after fetal testing identified an abnormality. The table below lists the outcomes for all postmarketing reports of exposure during pregnancy received during this report period.</p> <table><tr><th colspan="3">Spontaneous Reports of Exposure to Propecia during Pregnancy Received from Market Introduction (11-Sep-1997) to 18-Aug-2008 (n= 290[†])</th></tr><tr><th>Pregnancy Outcomes</th><th>Prospective</th><th>Retrospective</th></tr><tr><td>Elective abortion (n=16)</td><td>10</td><td>6</td></tr><tr><td>Spontaneous abortion (n=39)</td><td>2</td><td>37</td></tr><tr><td>Fetal death/stillbirth (n=4)</td><td>1</td><td>3</td></tr><tr><td>Ectopic Pregnancy (n=0)</td><td>0</td><td>0</td></tr><tr><td>Live births (n=62)</td><td>38</td><td>24</td></tr><tr><td>Unknown (n=169)</td><td colspan="2">169</td></tr><tr><th colspan="3">Congenital Anomalies*</th></tr><tr><th></th><th>Prospective</th><th>Retrospective</th></tr><tr><td>Congenital anomalies (n=21)</td><td>1</td><td>20</td></tr><tr><td>Genito-urinary[‡] (n= 11)</td><td>1</td><td>10</td></tr></table> <p>*Included in outcomes listed in table above [†]Note that total number of exposures will not equal the total number of reports, as some individual reports contain information on more than one pregnancy, or information of multiple fetuses. [‡]Included in congenital anomaly totals</p>	Spontaneous Reports of Exposure to Propecia during Pregnancy Received from Market Introduction (11-Sep-1997) to 18-Aug-2008 (n= 290 [†])			Pregnancy Outcomes	Prospective	Retrospective	Elective abortion (n=16)	10	6	Spontaneous abortion (n=39)	2	37	Fetal death/stillbirth (n=4)	1	3	Ectopic Pregnancy (n=0)	0	0	Live births (n=62)	38	24	Unknown (n=169)	169		Congenital Anomalies*				Prospective	Retrospective	Congenital anomalies (n=21)	1	20	Genito-urinary [‡] (n= 11)	1	10
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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

19

Important Identified Risk	MedDRA Preferred Terms:
Exposure during Pregnancy	Drug exposure during pregnancy
	<p>Of the 290 spontaneous reports of exposure to PROPECIA during pregnancy, the primary routes of exposure that have been reported to Merck include: semen (women's partner taking drug), dermal (through the woman's contact with crushed and/or broken tablets or through contact with intact tablets), oral (maternal ingestion), and inhalation of the powder from crushed tablets. More than one route of exposure was reported (e.g., handling tablets and inhalation) in a number of individual patients. Reports in which maternal exposure occurred through prescribed off-label use are discussed in detail in the next section (Details of Important Identified and Important Potential Risks: Off-Label Use in Women and Adolescents).</p> <p>Twenty-one reports of congenital anomalies were received by the Company (1 prospective report and 20 retrospective reports). No congenital anomalies were reported in patients exposed to PROPECIA through maternal ingestion. All congenital anomalies that were reported involved patients exposed to PROPECIA via semen. Of these 21 reports, 11 reports involve genitourinary abnormalities. All reports are summarized below.</p> <p>Of the 10 reports of congenital anomalies that did not involve a reported genitourinary event, all were retrospectively reported. Two cases of trisomy 21 were reported; the remaining 8 reports described isolated cases of Dandy-Walker syndrome, Prader-Willi syndrome, arteriovenous malformation, symbrachydactyly, "malformed arms", "numerous birth defects" unspecified, "heart abnormalism" unspecified, and an "undisclosed defect". No specific pattern of anomalies was identified.</p> <p>Eleven reports containing genitourinary congenital anomalies were reported in 11 live births. One report was received prospectively, the remaining 10 were retrospective.</p> <p>The single prospective report described a case of hydrocele.</p> <p>The retrospective reports describe a range of anomalies including "congenital genital malformation" (1), cryptorchism (1), enlarged urethral opening and pectus excavatum (1), and hypospadias (7).</p> <p>The 7 hypospadias reports are further described below.</p> <ul style="list-style-type: none"> • 1 case of hypospadias as the sole abnormality • 1 case in combination with ambiguous genitalia further evaluated by an endocrinologist who concluded that the congenital anomalies were clearly the result of a karyotype abnormality and that genetic testing revealed that "all of the child's Y chromosomes are abnormal". No further information regarding this chromosomal abnormality is available. • 1 case in combination with micropenis. Genetic studies were "negative" and the physician confirmed there was no congenital 5-alpha reductase deficiency.

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

20

Important Identified Risk	MedDRA Preferred Terms:
Exposure during Pregnancy	Drug exposure during pregnancy
	<ul style="list-style-type: none"> • 1 case in combination with male ambiguous deformed genitalia, "descended testicles" and an incomplete urethra. The infant's dihydrotestosterone levels were reported as normal. • 1 case in combination with a premature birth at 29 weeks, cryptorchism, and bilateral inguinal hernias. • 1 case in combination with a premature birth at 27-28 weeks and multiple anomalies including adrenal hypoplasia, bronchopulmonary dysplasia, male pseudohermaphrodite with hypogonadism, renal tubular disorder, and thymus disorder. The infant died. Pathology report: most likely explanation for the combination of findings is uteroplacental insufficiency. • 1 case in combination with cryptorchism and congenital chordee. <p>Available reports of potential exposure to finasteride in semen during pregnancy support the conclusions from clinical and preclinical studies that the amount of finasteride in semen is not clinically significant. There have been no prospective reports of hypospadias following potential exposure of the mother to finasteride via the semen, and the overall incidence of major congenital anomalies in these reports is less than the incidence of birth defects reported by Metropolitan Atlanta Congenital Defects Program (MACDP) in the United States background population [1548]. There are retrospective reports of hypospadias however; it is far more likely that these reports represent sporadic events that are unrelated to paternal use of finasteride. Hypospadias is a relatively common congenital anomaly with a reported incidence ranging from 0.8 to 8 cases per 1000 live male births [569]. Because of the relatively high background incidence of this abnormality, it is not unexpected that there will be cases of hypospadias that are unrelated to treatment in the offspring of men who are treated with finasteride during their partner's pregnancy.</p> <p>In conclusion, exposure of pregnant women to semen of men taking finasteride has not been demonstrated to constitute a risk to the developing male fetus. As indicated in the prescribing information for PROPECIA, administration of finasteride to women is contraindicated and there are clear statements concerning the potential risk of dermal exposure to the drug.</p>

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

21

Important Identified Risk	MedDRA Preferred Terms not applicable.
Off-label Use in women and adolescents	
	Clinical study data not applicable.
Seriousness/Outcomes	Not applicable
Severity and Nature of Risk	Not applicable
Frequency With 95% CI	Not applicable
Background Incidence/Prevalence	Not applicable
Risk Groups or Risk Factors	Not applicable
Potential Mechanisms	Not applicable
Preventability	Not applicable. Label indicates medication not indicated in women or in men under age 18.
Potential Public Health Impact of Safety Concern	The safety profile of PROPECIA related to off-label use in women and adolescents has been well-characterized since market introduction, and the public health impact is not expected to change in the future. Cumulative analyses of postmarketing data for off-label use in women and adolescents (see below) reveals minimal public health impact.
Evidence Source	WAES database
Regulatory Action Taken	None
Postmarketing Data	<p><u>Off-Label Use in Women / Adolescents</u></p> <p>The Merck Worldwide Adverse Experience System (WAES) database was searched for spontaneous reports from healthcare providers (HCPs), including those received via regulatory agencies and consumers from market introduction (11-Sep-1997) to 18-Aug-2008 in patients treated with finasteride 0.2 mg and 1 mg tablets and in which the gender of the patient was recorded as being female; and adolescents (age 13 to 17), male and female gender. Reports included in this review are women and adolescents who have been prescribed finasteride 0.2 mg and 1 mg tablets. Reports of accidental exposure and exposure via semen are excluded.</p> <p><u>Off-Label Use in Women</u></p> <p>A total of 371 spontaneous reports were identified from this search. All reports were in women ≥ 18 years of age or age not recorded. Nineteen of the 371 spontaneous reports identified met the regulatory criteria for a serious report; the remaining 352 reports were non-serious. One hundred and twenty-seven reports were received from healthcare providers (HCPs) including regulatory agencies and 244 reports were received from consumers. One hundred and sixty-one of 371 patients (43%) patients were between 18 to 64 years of age and 64/371 (17%) patients were ≥ 65 years of age; age was not reported in the remaining 146/371 (40%) of the patients. The greatest percentage of the patients fell into the age group 45-54 years: 58/371 (16%). With the exception of the high reporting rate at market introduction, which is expected, reporting rates of ADRs have remained consistent over time, at well under 10 per 100,000 patient-years of treatment (PYT). See below.</p>

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

22

Important Identified Risk Off-label Use in women and adolescents	MedDRA Preferred Terms not applicable.																																							
	<p>Reported off-label reasons for use with finasteride therapy included alopecia (in women), hirsutism, hormonal imbalance, polycystic ovaries, testosterone high, and scalp pain.</p> <p>Off-label Use in Women-Reports by Year/Reporting Rate</p> <table><tr><th>Year</th><th>Number of Spontaneous Reports</th><th>Reporting Rate per 100,000 years exposure</th></tr><tr><td>1998</td><td>37</td><td>19.8</td></tr><tr><td>1999</td><td>36</td><td>8.2</td></tr><tr><td>2000</td><td>46</td><td>9.9</td></tr><tr><td>2001</td><td>26</td><td>5.3</td></tr><tr><td>2002</td><td>22</td><td>4.4</td></tr><tr><td>2003</td><td>23</td><td>4.4</td></tr><tr><td>2004</td><td>34</td><td>6.3</td></tr><tr><td>2005</td><td>46</td><td>8.3</td></tr><tr><td>2006</td><td>32</td><td>5.2</td></tr><tr><td>2007</td><td>43</td><td>6.5</td></tr><tr><td>2008†</td><td>26</td><td>6.8</td></tr><tr><td>Total</td><td>371</td><td>6.9</td></tr></table> <p>† Reports received through 18-Aug-2008 * Drug distribution data calculated through 31-Jul-2008</p> <p>Of the 371 reports of female off-label use, 112 reports described no ADR beside the medication error or off-label use itself. The following tables outline the twenty most frequent ADRs and the twenty most frequent serious ADRs in the remaining 259 reports.</p>	Year	Number of Spontaneous Reports	Reporting Rate per 100,000 years exposure	1998	37	19.8	1999	36	8.2	2000	46	9.9	2001	26	5.3	2002	22	4.4	2003	23	4.4	2004	34	6.3	2005	46	8.3	2006	32	5.2	2007	43	6.5	2008†	26	6.8	Total	371	6.9
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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

23

Important Identified Risk Off-label Use in women and adolescents	MedDRA Preferred Terms not applicable.																																														
	<p data-bbox="857 388 1166 436" style="text-align: center;">Off-label Use in Women Twenty Most Frequent ADRs</p> <table border="1" data-bbox="685 464 1104 1276"> <thead> <tr> <th data-bbox="691 472 1019 499">ADR</th><th data-bbox="1019 472 1097 499">N</th></tr> </thead> <tbody> <tr><td data-bbox="691 506 1019 533">Drug administration error</td><td data-bbox="1019 506 1097 533">167</td></tr> <tr><td data-bbox="691 539 1019 567">Alopecia</td><td data-bbox="1019 539 1097 567">34</td></tr> <tr><td data-bbox="691 573 1019 600">Drug ineffective</td><td data-bbox="1019 573 1097 600">26</td></tr> <tr><td data-bbox="691 606 1019 634">No ADR</td><td data-bbox="1019 606 1097 634">12</td></tr> <tr><td data-bbox="691 640 1019 667">Off-label use</td><td data-bbox="1019 640 1097 667">11</td></tr> <tr><td data-bbox="691 674 1019 737">Drug exposure during pregnancy</td><td data-bbox="1019 674 1097 737">10</td></tr> <tr><td data-bbox="691 743 1019 770">Hypertrichosis</td><td data-bbox="1019 743 1097 770">10</td></tr> <tr><td data-bbox="691 777 1019 804">Pruritus</td><td data-bbox="1019 777 1097 804">10</td></tr> <tr><td data-bbox="691 810 1019 837">Hair texture abnormal</td><td data-bbox="1019 810 1097 837">7</td></tr> <tr><td data-bbox="691 844 1019 871">Nausea</td><td data-bbox="1019 844 1097 871">7</td></tr> <tr><td data-bbox="691 877 1019 905">Weight increased</td><td data-bbox="1019 877 1097 905">7</td></tr> <tr><td data-bbox="691 911 1019 938">Rash</td><td data-bbox="1019 911 1097 938">7</td></tr> <tr><td data-bbox="691 945 1019 972">Asthenia</td><td data-bbox="1019 945 1097 972">6</td></tr> <tr><td data-bbox="691 978 1019 1005">Libido decreased</td><td data-bbox="1019 978 1097 1005">6</td></tr> <tr><td data-bbox="691 1012 1019 1039">Hot flush</td><td data-bbox="1019 1012 1097 1039">6</td></tr> <tr><td data-bbox="691 1045 1019 1073">Breast tenderness</td><td data-bbox="1019 1045 1097 1073">6</td></tr> <tr><td data-bbox="691 1079 1019 1106">Headache</td><td data-bbox="1019 1079 1097 1106">6</td></tr> <tr><td data-bbox="691 1113 1019 1140">Fatigue</td><td data-bbox="1019 1113 1097 1140">5</td></tr> <tr><td data-bbox="691 1146 1019 1173">Therapeutic response decreased</td><td data-bbox="1019 1146 1097 1173">5</td></tr> <tr><td data-bbox="691 1180 1019 1207">Breast enlargement</td><td data-bbox="1019 1180 1097 1207">4</td></tr> <tr><td data-bbox="691 1213 1019 1241">Other</td><td data-bbox="1019 1213 1097 1241">205</td></tr> <tr><td data-bbox="691 1247 1019 1274">Total</td><td data-bbox="1019 1247 1097 1274">557</td></tr> </tbody> </table>	ADR	N	Drug administration error	167	Alopecia	34	Drug ineffective	26	No ADR	12	Off-label use	11	Drug exposure during pregnancy	10	Hypertrichosis	10	Pruritus	10	Hair texture abnormal	7	Nausea	7	Weight increased	7	Rash	7	Asthenia	6	Libido decreased	6	Hot flush	6	Breast tenderness	6	Headache	6	Fatigue	5	Therapeutic response decreased	5	Breast enlargement	4	Other	205	Total	557
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11-Feb-2009

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

24

Important Identified Risk Off-label Use in women and adolescents	MedDRA Preferred Terms not applicable.																																												
	<p style="text-align: center;">Off-label Use in Women Twenty Most Frequent Serious ADRs</p> <table border="1"> <thead> <tr> <th>ADR</th><th>N</th></tr> </thead> <tbody> <tr><td>Breast cancer</td><td>3</td></tr> <tr><td>Abortion induced</td><td>2</td></tr> <tr><td>Breast calcifications</td><td>2</td></tr> <tr><td>Neoplasm</td><td>2</td></tr> <tr><td>Overdose</td><td>2</td></tr> <tr><td>Abortion spontaneous</td><td>1</td></tr> <tr><td>Blood creatinine increased</td><td>1</td></tr> <tr><td>Breast mass</td><td>1</td></tr> <tr><td>Transient ischaemic attack</td><td>1</td></tr> <tr><td>Vulval neoplasm</td><td>1</td></tr> <tr><td>Vaginal haemorrhage</td><td>1</td></tr> <tr><td>Uterine disorder</td><td>1</td></tr> <tr><td>Thrombocytopenia</td><td>1</td></tr> <tr><td>Ovarian cyst</td><td>1</td></tr> <tr><td>Cerebrovascular accident</td><td>1</td></tr> <tr><td>Fatigue</td><td>1</td></tr> <tr><td>Glomerular filtration rate decreased</td><td>1</td></tr> <tr><td>Major depression</td><td>1</td></tr> <tr><td>Mammogram abnormal</td><td>1</td></tr> <tr><td>Other</td><td>0</td></tr> <tr><td>Total</td><td>25</td></tr> </tbody> </table> <p>Reports related to hair growth or hair loss, exposure during pregnancy and/or breast related ADRs; medication error, off-label use, and drug ineffective make up the majority of the reports.</p> <p>A review of the serious reports revealed that many were considered serious due to the event of overdose, pregnancy outcome, or breast cancer and related events (breast calcifications, breast mass and neoplasm). Background gynecological and/or breast related ADRs would be anticipated in a female population. A review of these individual reports did not reveal any new safety signals.</p> <p>Off-label Use in Women: Pregnancy Reports</p> <p>The reports detailed in this section contributed to the overall number of pregnancies (290) in the cumulative review presented in the previous section (Details of Important Identified and Important Potential Risks: Exposure During Pregnancy); but represent only those cases of PROPECIA exposure during pregnancy that occurred as a result of prescribed off-label use. Eleven reports of</p>	ADR	N	Breast cancer	3	Abortion induced	2	Breast calcifications	2	Neoplasm	2	Overdose	2	Abortion spontaneous	1	Blood creatinine increased	1	Breast mass	1	Transient ischaemic attack	1	Vulval neoplasm	1	Vaginal haemorrhage	1	Uterine disorder	1	Thrombocytopenia	1	Ovarian cyst	1	Cerebrovascular accident	1	Fatigue	1	Glomerular filtration rate decreased	1	Major depression	1	Mammogram abnormal	1	Other	0	Total	25
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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

25

Important Identified Risk Off-label Use in women and adolescents	MedDRA Preferred Terms not applicable.
	<p>off-label exposure to PROPECIA (1 mg) during pregnancy were identified. All 11 reports represented oral exposure. Ten reports were prospective and 1 report was retrospective. Prospective reports are those received before the outcome of the pregnancy is known, while retrospective reports are received after the outcome of the pregnancy is known. A report is classified as retrospective if a probable outcome had been identified prior to delivery by diagnostic testing such as ultrasound. Retrospective reporting of exposures is subject to selective reporting bias in that birth defects are more likely to be reported than normal foetal outcomes. Because of the bias toward reporting abnormal outcomes, retrospective reports are analyzed separately from prospective reports.</p> <p>Prospective report overview</p> <ul style="list-style-type: none"> • In 6 of the 10 prospective pregnancy reports, no pregnancy outcome was reported • 2 patients had elective terminations • 2 patients experienced live births further described as "baby was fine", and liveborn male, no congenital anomalies or complications. <p>Retrospective report overview</p> <ul style="list-style-type: none"> • In this 1 report, a 37 year old female interrupted therapy with finasteride 2 months prior to her LMP, became pregnant and subsequently in her 5th week of pregnancy experienced a spontaneous abortion. <p>Off-Label Use in Adolescents 12 to 17 years</p> <p>A total of 35 spontaneous reports were identified from this search. All were male; there were no reports of off-label use in females age 12-17 years. Six of the 35 spontaneous reports identified met the regulatory criteria for a serious report; the remaining 29 reports were non-serious. Nineteen reports were received from healthcare providers (HCPs) including regulatory agencies and 16 reports were received from consumers. Age range of the patients was 13-17 years with a majority being 17 years old 27/35 (77%) Reporting rates of ADRs remained consistently low over time and the majority of reports were received from the United States. All patients were prescribed finasteride therapy for the treatment of alopecia.</p>

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

26

Important Identified Risk Off-label Use in women and adolescents	MedDRA Preferred Terms not applicable.																																							
	<p>Off-Label Use in Adolescents Reports by Year/Reporting Rate</p> <table><tr><th>Year</th><th>Number of Spontaneous Reports</th><th>Reporting Rate per 100,000 years exposure</th></tr><tr><td>1998</td><td>3</td><td>1.6</td></tr><tr><td>1999</td><td>2</td><td>0.45</td></tr><tr><td>2000</td><td>2</td><td>0.43</td></tr><tr><td>2001</td><td>3</td><td>0.60</td></tr><tr><td>2002</td><td>5</td><td>1.0</td></tr><tr><td>2003</td><td>6</td><td>1.1</td></tr><tr><td>2004</td><td>3</td><td>0.55</td></tr><tr><td>2005</td><td>3</td><td>0.54</td></tr><tr><td>2006</td><td>1</td><td>0.16</td></tr><tr><td>2007</td><td>3</td><td>0.45</td></tr><tr><td>2008†</td><td>4</td><td>1.0</td></tr><tr><td>Total</td><td>35</td><td>0.65</td></tr></table> <p>† Reports received through 18-Aug-2008 * Drug distribution data calculated through 31-Jul-2008</p> <p>The following tables outline the twenty most frequent ADRs and the most frequent serious ADRs in these 35 reports.</p>	Year	Number of Spontaneous Reports	Reporting Rate per 100,000 years exposure	1998	3	1.6	1999	2	0.45	2000	2	0.43	2001	3	0.60	2002	5	1.0	2003	6	1.1	2004	3	0.55	2005	3	0.54	2006	1	0.16	2007	3	0.45	2008†	4	1.0	Total	35	0.65
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11-Feb-2009

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

27

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

28

Important Identified Risk Off-label Use in women and adolescents	MedDRA Preferred Terms not applicable.
	<p>total of 9 ADRs in 6 patients) revealed that most were considered serious due to the event of overdose. One report described a described a 16 year old male who approximately 1 month after initiating therapy with finasteride 1 mg daily experienced a personality change, suicidal ideation and was depressed. Therapy with finasteride was discontinued. No information regarding concomitant medication, or medical history was provided. Outcomes to the reported events were unknown.</p> <p>The majority of AE reports involving use of finasteride in adolescents reflect the AE profile seen in patients with regular use of finasteride. A review of these individual reports did not reveal any new safety signals.</p> <p>The MAH has been vigilant in its labeling for the compound (in the SPC, patient information and on the package) in terms of deterring off-label use. Regarding women in particular, the product circular stresses not only the safety issues relating to potential exposure to finasteride during pregnancy, but also the lack of efficacy demonstrated in a study in post-menopausal women.</p>

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11-Feb-2009

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

29

Important Potential Risk	MedDRA Preferred Terms
Persistence of erectile dysfunction	Erectile dysfunction Persistence of erectile dysfunction
Seriousness/Outcomes	In the Phase III controlled studies (P087, 089 and 092; N=945 finasteride, N=934 placebo) the following terms for erectile dysfunction were reported: impotence, erection dysfunction, erection difficulty, erections incomplete, morning erections decreased, and erection firmness decreased. No serious drug-related adverse experiences Discontinued due to drug related erectile dysfunction: Finasteride: 0.6% Placebo: 0.5% For all these men the erectile dysfunction resolved off drug.
Severity and Nature of Risk	Phase III controlled studies (087,089, & 092): Finasteride : 45.5 % mild; 54.5% moderate; severe 0 % Placebo: 28.6% mild; 57.1% moderate; 14.3% severe
Frequency With 95% CI	Phase III controlled studies (087,089, & 092): Drug-related Finasteride: 12 (1.3%) Placebo: 7 (0.7%)
Background Incidence/Prevalence	Epidemiologic reports suggest that in general between 5 and 20% of men have moderate to severe erectile dysfunction. [1528] While there have been higher reports of prevalence, these estimates were usually in specific populations (e.g., diabetics or older men). The wide variability in prevalence estimates may be attributed to differences in definitions of erectile dysfunction and ascertainment methods. Incidence estimates for erectile dysfunction range from 25.9 to 98.6 cases per 1000 person-years. [1214; 1553]
Risk Groups or Risk Factors	The prevalence of erectile dysfunction increases with age even after adjustment for potential confounders. Factors associated with an increased risk of erectile dysfunction include increasing age, chronic disease such as diabetes and atherosclerosis, obesity, smoking, substance abuse (e.g., alcohol), certain medications, certain medical procedures, stress and anxiety. [1213; 1534]
Potential Mechanisms	Not known
Preventability	Not known
Potential Public Health Impact of Safety Concern	The safety profile of PROPECIA related to erectile dysfunction has been well characterized, and is included in the product label; it is not expected to change in the future. Cumulative analysis of postmarketing data since market introduction of reports of erectile dysfunction (see below) indicate that only 3.8% of reports of erectile dysfunction are considered serious, and that severity is based upon the consumer or HCP considering the ED disabling, or considering it an other important medical event, indicating minimal public health impact. Analysis of reports of persistent erectile dysfunction (see below) reveals minimal public health impact.
Evidence Source	Summary of Clinical Safety (Phase III controlled studies) WAES database

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

30

Important Potential Risk	MedDRA Preferred Terms
Persistence of erectile dysfunction	Erectile dysfunction Persistence of erectile dysfunction
Regulatory Action Taken	None
Postmarketing	<p>The Worldwide Adverse Experience System (WAES) database was searched for spontaneous reports of erectile dysfunction from health care providers (including regulatory agencies) and from consumers in patients on therapy with finasteride 1 mg and 0.2 mg tablet (PROPECIA) from market introduction to 18-Aug-2008. Postmarketing preferred terms identified were: erectile dysfunction, male sexual dysfunction, organic erectile dysfunction and sexual dysfunction.</p> <p>A total of 2134 [82, (3.8%) serious] reports were identified. Six hundred and twenty-one reports were received from HCP's and 1513 were from consumers. Review of the 82 serious reports revealed 7 reports where the report met the regulatory criteria for a serious report due to an event other than ED, e.g., overdose, cancer. The majority of the remaining reports were either considered serious because the consumer or healthcare provider considered the ED event disabling and/or an "other important medical event". No serious sequelae directly related to ED were identified in any reports.</p> <p>To identify cases that may represent persistent ED the MAH reviewed the reports with an outcome of not recovered in whom finasteride was discontinued. Two hundred and seventy-eight reports were identified; 25/278 (9%) were reported as serious events of ED.</p> <p>In a majority of these 278 cases, critical data were not reported (i.e., time from discontinuation of finasteride to time patient reported as not recovered, concurrent medications, medical history) limiting the value of these reports in assessing the relationship of finasteride therapy to persistence of erectile dysfunction. Additionally, in the majority of these 278 reports, the information was reported to the Company within 1 day to several weeks from the time of discontinuation of therapy. Despite multiple attempts to obtain follow up information in accordance with the Company's standard procedures, no further information was provided. Thus, the ability to assess the overall trend in the time to recovery as well as overall outcome information relative to erectile dysfunction is limited, as longer term outcome data are not available in the large majority of cases. In addition, a number of cases were confounded by concurrent medical conditions that may affect erectile dysfunction, such as diabetes, psychiatric illness, or advancing age. Finally, many of the reports lacked information pertaining to diagnostic evaluation such as urological testing or thorough data regarding social and medical history. As a result, other environmental, biological or psychological factors that can potentially influence persistence of erectile dysfunction are difficult to rule out.</p>

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

31

Important Potential Risk	MedDRA Preferred Terms
Persistence of erectile dysfunction	Erectile dysfunction Persistence of erectile dysfunction
	<p>Within this cohort of 278 reports are cases that do appear to describe persistent erectile dysfunction after discontinuation of finasteride therapy, without evidence of other confounding variables. Three such representative cases are described below.</p> <p>WAES 00111978 describes a 35 year old male who was started on treatment with finasteride 1 mg daily for the treatment of hair loss. After approximately 6 months of treatment the patient experienced impotence and decreased libido. Therapy with finasteride was eventually discontinued after 13 months of treatment. The patient reported he had been off finasteride for 4 months and his symptoms continued.</p> <p>WAES 0611USA04853 describes a 38 year old male with no pertinent medical history, no drug allergies, and on no concomitant medication who was placed on therapy with finasteride 1 mg daily for the treatment of hair loss. Subsequently he noticed his erections were not as firm. The patient continued therapy with finasteride for 1 year. The patient underwent a complete blood panel, results negative; Doppler study and "every urological study", results not provided. Approximately 1 year after discontinuation of therapy with finasteride, the patient was unable to obtain an erection.</p> <p>WAES 0707SGP00011 describes a male, age not reported who was placed on therapy with finasteride 1 mg daily for the treatment of alopecia. Approximately 3 months after initiating therapy with finasteride, the patient complained of erectile dysfunction and itching. Finasteride was discontinued on 14-Mar-2007. In July 2007 the patient was referred to an andrologist for evaluation of erectile dysfunction and was treated with HCG 5000 units/3 x week.</p>

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

32

Important Potential Risk Male Infertility	MedDRA Preferred Terms Infertility
Seriousness/Outcomes	<p>In the Phase III controlled studies (P087, 089 and 092; N=945 finasteride, N=934 placebo) there were no reports of infertility, male infertility, impaired fertility, or unable to father children. At the start of these Phase III studies and the first extension studies, men whose sexual partner(s) was/were pregnant or planning pregnancy within the 12-month study period were excluded from the study. This exclusion was not included in subsequent new and extension studies when data from a study in pregnant rhesus monkeys demonstrated that the exposure of pregnant women to the small amount of finasteride in the semen of men taking finasteride 1 mg/day is not considered a risk for the developing fetus. (See Section 1.1.1 <u>Nonclinical Safety Concerns.</u>)</p> <p>In the Phase III pivotal studies there was no indication that finasteride had a negative impact on male fertility. As noted above in the 60 months of the Phase III Pivotal studies (087 & 089), the incidence rate of pregnancy in the patient's sexual partner per 100 treatment years was somewhat higher for finasteride-treated men than for placebo-treated men (1.26 versus 0.71, respectively).</p> <p>Finasteride has no affinity for the androgen receptor and no direct androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of Type II 5α-reductase by finasteride blocks the peripheral conversion of testosterone to DHT, which leads to significant decreases in serum and tissue DHT concentrations while maintaining mean circulating levels of serum testosterone and estradiol within the physiologic range. No increase relative to baseline was observed in men treated with finasteride 1 mg for 48 weeks. Finasteride has also been shown not to alter pituitary responsiveness to gonadotropin-releasing hormone in normal subjects.</p> <p>In a pooled analysis of safety data from men randomized into the Phase III Studies (087, 089 & 092) (Finasteride N=945; Placebo N=934) supporting the marketing application for finasteride 1 mg (PROPECIA), no significant differences compared to placebo in luteinizing hormone (LH) or follicle-stimulating hormone (FSH) were observed. In a separate safety study (MK-0906 094), a subset of 79 men were randomized to receive 1 mg finasteride or placebo for 48 weeks followed by a 60-week off-drug period (total study duration of 108 weeks) for collection and analysis of sequential semen samples. Compared to placebo, finasteride 1 mg/day had no significant effect on sperm concentration, total sperm per ejaculate, sperm motility or morphology at any time. At the end of the on-drug period (48 weeks), median ejaculate volume was decreased by -0.3 mL (-10.9%, 95% CI -18.9 to 4.3) in the finasteride group and by -0.2 mL (-7.8%, 95% CI -25.5 to 3.9) in the placebo group, with a between-treatment group difference of -0.03 mL (1%, 90% CI -10.4 to 13.1, p=0.915). Analysis of data through Week 108 confirmed that the small fluctuations observed in semen parameters</p>

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

33

Important Potential Risk Male Infertility	MedDRA Preferred Terms Infertility
	<p>receiving 1 mg finasteride daily during treatment were similar to changes observed in the placebo group and consistent with normal intra-subject variability. [942]</p> <p>This study demonstrated that finasteride 1 mg daily compared to placebo for 48 weeks did not affect sperm concentration, total sperm per ejaculate, percent motile sperm or percent sperm with normal morphology in ejaculated semen.</p> <p>In addition to the analyses described above, a tertile analysis of semen parameters was performed. Based on these analyses, there was no suggestion of an effect of finasteride in men with more marginal parameters at baseline. Subjects with the most marginal baseline values for each semen parameter, who can serve as a model for those who may be subfertile, demonstrated less change from baseline over time than those with higher values at baseline. Further, review of data for all patients whose values were below the lower limit of normal during the 48-week treatment period demonstrated that the number of patients with values below the normal range was similar between the finasteride and placebo treatment groups, with the lowest measured value for most parameters found in patients receiving placebo. Because semen parameters provide an assessment of testicular function, these data support the conclusion that finasteride 1 mg does not adversely affect fertility in any subpopulation of men, including subfertile men.</p> <p>Taken together, these data indicate that treatment with finasteride does not interfere with normal negative feedback regulation of the hypothalamic-pituitary-gonadal axis, supporting normal Sertoli cell function and Leydig and Sertoli cell interactions in subjects treated with finasteride 1 mg.</p>
Severity and Nature of Risk	Not known
Frequency With 95% CI	No data available.
Background Incidence/Prevalence	<p>Infertility is defined as the inability to achieve conception despite one year of frequent unprotected intercourse. An estimated 10-15% of couples in the United States are considered infertile. Major causes of infertility include male factors (20%), and the female factors (35-38%) of ovarian dysfunction, tubal disease, endometriosis, and uterine or cervical disease. In 20-27% of couples both male and female factors contribute to infertility and in 15% of couples the cause for infertility is unexplained. [1518; 1520].</p> <p>Causes of infertility in men include testicular disease (primary hypogonadism), hypothalamic pituitary disease (secondary hypogonadism), post-testicular defects (disorders of sperm transport), and in nearly one half of male patients the cause of infertility remains unclear. Recognizable causes of infertility are found in only 30-50% of the cases. [1517]</p>

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

34

Important Potential Risk Male Infertility	MedDRA Preferred Terms Infertility
Risk Groups or Risk Factors	Known factors associated with a higher risk of male factor infertility include androgen insensitivity, congenital or developmental testicular disorders (e.g., Klinefelter syndrome), cryptorchidism, medications (e.g., alkylating agents, antiandrogens, cimetidine, ketoconazole, spironolactone), orchitis, radiation exposure, testicular trauma, varicocele, Y chromosome defect. [1520]
Potential Mechanisms	Not known
Preventability	No data available
Potential Public Health Impact of Safety Concern	Analysis of clinical trial data and of postmarketing data since market introduction does not indicate that male infertility in patients on PROPECIA represents a potentially significant impact on public health. Analysis of cumulative postmarketing data since market introduction indicates a low reporting rate, and it is not anticipated that this will change in the future.
Evidence Source	Summary of clinical safety (Phase III controlled studies) WAES database
Regulatory Action Taken	None
Postmarketing	<p>The Worldwide Adverse Experience System (WAES) database was searched for spontaneous reports of male infertility and related infertility events in patients treated with PROPECIA primary suspect therapy received from HCPs, including regulatory agencies, and consumers from market introduction (11-Sep-1997) through 18-Aug-2008. Postmarketing preferred terms identified were: sperm count decreased, azoospermia, infertility, spermatozoa progressive motility decreased, spermatozoa progressive motility abnormal, infertility male, spermatozoa abnormal, sperm analysis abnormal, teratospermia, spermatogenesis abnormal, asthenospermia, sperm count zero, spermatozoa morphology abnormal, aspermia, sperm count abnormal.</p> <p>A total of 187 reports (15 serious, 8%) have been received with one or more of the Adverse Drug Reactions (ADRs) noted below. One hundred and ten reports were received from HCP's and 77 were from consumers.</p>

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

35

Important Potential Risk Male Infertility	MedDRA Preferred Terms Infertility																																				
	<table border="1"> <thead> <tr> <th data-bbox="695 415 1003 443">MedDRA Preferred term</th><th data-bbox="1015 415 1317 443">Number of ADRs* (Serious)</th></tr> </thead> <tbody> <tr><td data-bbox="695 445 1003 472">Sperm count decreased</td><td data-bbox="1015 445 1317 472">63 (2)</td></tr> <tr><td data-bbox="695 474 1003 501">Azoospermia</td><td data-bbox="1015 474 1317 501">43 (6)</td></tr> <tr><td data-bbox="695 504 1003 531">Infertility</td><td data-bbox="1015 504 1317 531">41 (3)</td></tr> <tr><td data-bbox="695 533 1003 596">Spermatozoa progressive motility decreased</td><td data-bbox="1015 533 1317 596">26 (1)</td></tr> <tr><td data-bbox="695 598 1003 661">Spermatozoa progressive motility abnormal</td><td data-bbox="1015 598 1317 661">12 (0)</td></tr> <tr><td data-bbox="695 663 1003 690">Infertility male</td><td data-bbox="1015 663 1317 690">10 (1)</td></tr> <tr><td data-bbox="695 693 1003 720">Spermatozoa abnormal</td><td data-bbox="1015 693 1317 720">8 (1)</td></tr> <tr><td data-bbox="695 722 1003 749">Sperm analysis abnormal</td><td data-bbox="1015 722 1317 749">7 (0)</td></tr> <tr><td data-bbox="695 751 1003 779">Teratospermia</td><td data-bbox="1015 751 1317 779">7 (1)</td></tr> <tr><td data-bbox="695 781 1003 808">Spermatogenesis abnormal</td><td data-bbox="1015 781 1317 808">4 (1)</td></tr> <tr><td data-bbox="695 810 1003 837">Asthenospermia</td><td data-bbox="1015 810 1317 837">2 (0)</td></tr> <tr><td data-bbox="695 840 1003 867">Sperm count zero</td><td data-bbox="1015 840 1317 867">2 (0)</td></tr> <tr><td data-bbox="695 869 1003 932">Spermatozoa morphology abnormal</td><td data-bbox="1015 869 1317 932">2 (0)</td></tr> <tr><td data-bbox="695 934 1003 961">Aspermia</td><td data-bbox="1015 934 1317 961">1 (0)</td></tr> <tr><td data-bbox="695 963 1003 991">Sperm count abnormal</td><td data-bbox="1015 963 1317 991">1 (0)</td></tr> <tr><td data-bbox="695 993 1003 1020">Total Events</td><td data-bbox="1015 993 1317 1020">229 (16)</td></tr> <tr><td data-bbox="695 1022 1003 1050">Total Reports</td><td data-bbox="1015 1022 1317 1050">187 (15)</td></tr> </tbody> </table> <p data-bbox="683 1010 1325 1056">*A single report may include more than one ADR, therefore the sum of the ADRs can be greater than the total number of reports.</p> <p data-bbox="683 1083 1325 1245">Of the 187 total reports received describing male infertility and related ADRs, 40 reports described the patient as recovered/recovering from infertility, 41 reports described the patients as not recovered at the time of reporting and the outcome of male infertility and related events in the majority of reports (106) was unknown at the time of reporting.</p> <p data-bbox="683 1272 1325 1465">Review of the 15 serious reports revealed most did not include important clinical information such as baseline fertility evaluation/sperm analysis, or details regarding concurrent conditions and/or concomitant therapies which could predispose to infertility thus limiting a proper causality assessment. In addition, no details of evaluation for female infertility factors were provided in these reports.</p> <p data-bbox="683 1493 1325 1545">Report distribution by year and corresponding reporting rates are presented below revealing no major change over time.</p>	MedDRA Preferred term	Number of ADRs* (Serious)	Sperm count decreased	63 (2)	Azoospermia	43 (6)	Infertility	41 (3)	Spermatozoa progressive motility decreased	26 (1)	Spermatozoa progressive motility abnormal	12 (0)	Infertility male	10 (1)	Spermatozoa abnormal	8 (1)	Sperm analysis abnormal	7 (0)	Teratospermia	7 (1)	Spermatogenesis abnormal	4 (1)	Asthenospermia	2 (0)	Sperm count zero	2 (0)	Spermatozoa morphology abnormal	2 (0)	Aspermia	1 (0)	Sperm count abnormal	1 (0)	Total Events	229 (16)	Total Reports	187 (15)
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11-Feb-2009

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

36

Important Potential Risk Male Infertility	MedDRA Preferred Terms Infertility																																							
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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

37

Important Potential Risk Depressive Disorders	MedDRA Preferred Terms Depression
Seriousness/Outcomes	In the Phase III controlled studies (P087, 089 and 092; N=945 finasteride, N=934 placebo), the following terms for depression and depressive disorders were reported: depression, increased depression, and intermittent depression. No serious adverse experiences were reported.
Severity and Nature of Risk	Phase III controlled studies (P087, 089 and 092; N=945 finasteride, 934 placebo) Finasteride : 71.4 % mild; 28.6% moderate Placebo: 100% moderate
Frequency With 95% CI	Phase III controlled studies (P087, 089 and 092; N=945 finasteride, 934 placebo) Finasteride: 7 (0.7%) Placebo: 8 (0.9%)
Background Incidence/Prevalence	The incidence and prevalence of depressive disorders in males with androgenic alopecia is not available. However, in studies of the general population, estimates of the incidence of depressive disorders have ranged from 2.8 to 14.7 per 1000 person years [1558; 1559]. Lifetime risk for mood disorders (DSM criteria) for US males is 14.9%. Major depression varies from 3.4% (past year) to as high as 17% (lifetime). Emergency department (ED) estimates of suicide attempt (overall) is 1.5 per 1000 ED visits, with a greater occurrence in females. Completed suicide (lifetime risk) occurs in 11.1/100,000 total population in the US. Males are much more likely to complete suicide compared to females. In addition rates are highest in whites and native Americans (19.6 and 18.7 per 100,000 population respectively).
Risk Groups or Risk Factors	Both psychosocial and biological factors have been reported to be associated with depression in men. Psychological factors such as negative views toward self, experience and future may play a role in depressive symptom manifestation. Social factors such as the chronic stress, death of a spouse, sudden onset of physical illness, lack of social support and retirement have also been reported to contribute to depression. Biological factors include may include hereditary factors, neuroanatomic changes, neurotransmitter abnormalities, dysregulation of endocrine function or circadian rhythms (e.g., sleep). [1539]
Potential Mechanisms	Not known
Preventability	Not known
Potential Public Health Impact of Safety Concern	The impact of depression in patients on PROPECIA does not appear to have a significant impact on public health. The Company continues to monitor reports of depression in patients on PROPECIA. As indicated in the cumulative analysis of postmarketing data since market introduction (see below), the reporting rate of depressive disorders in patients on PROPECIA is low and comparable to expected background rates. It is not expected that this will change in the future.

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

38

Important Potential Risk Depressive Disorders	MedDRA Preferred Terms Depression
Evidence Source	Summary of Clinical Safety (Phase III controlled studies) WAES database
Regulatory Action Taken	None
Postmarketing Data	<p>The Worldwide Adverse Experience System (WAES) database was searched for spontaneous reports of depression and related depression events in patients treated with PROPECIA primary suspect therapy received from HCPs, including regulatory agencies, and consumers from market introduction (11-Sep-1997) through 18-Aug-2008. A total of 218 spontaneous reports were identified. Postmarketing preferred terms identified were: depression, depressed mood, depressive symptom, suicidal ideation, depression suicidal, major depression, suicide attempt.</p> <p>Report distribution by year and corresponding reporting rates are presented below showing low and stable reporting rates following the first year after product launch, an increase in reporting frequency in year 2006, followed by a slight decline in 2007. The estimated reporting rate of depressive disorders is 4.0 events per 100,000 patient-years of exposure. While there is a paucity of incidence data of depression and depressive-related disorders in the general population, the World Health Organization has reported a global age-adjusted incidence rate (per 100,000 population) of 3199 in males (range: 2028-4294 per 100,000 population) [1561]. While these rates are not directly comparable, it does give some context as to the low occurrence of depressive disorders observed in patients on PROPECIA. The highest reporting rate in 1998 is associated with the product launch worldwide and the related increased initial spontaneous reporting [1488].</p> <p>The 42 reports received in 2006 were reviewed to identify factors that may have contributed to the increased reporting rate. Two factors have been identified.</p> <ul style="list-style-type: none"> • In January 2006, PROPECIA (finasteride 1 mg and 0.2 mg tablet) was launched in Japan. A number of reports (8) were received from Japan during 2006; this is characteristic of the Weber effect [1488]. In addition, during the first year of product approval in Japan, reports of adverse experiences are actively solicited as part of an Early Post-marketing Phase Vigilance (EPPV) program and are thus not truly spontaneous reports. • In 2006, the MAH received a letter from a consumer that outlined a number of consumer-reported events; the author of this letter stated that he had gathered his information from a consumer-driven website on which patients were asked to "rate" the drugs that they took. The author claimed there were multiple consumer-reported events of ADRs related to PROPECIA on the website. A list of all events from this website was obtained by the MAH and was reviewed. These were all consumer-generated, and all had minimal information

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

39

Important Potential Risk Depressive Disorders	MedDRA Preferred Terms Depression																																																											
	<p>that would have allowed any assessment of causality with respect to PROPECIA.</p> <ul style="list-style-type: none">In summary for 2006:<ul style="list-style-type: none">42 spontaneous reports of depressive disorders were received by the MAH8 of these reports were received from Japan as part of their EPPV program in the first year of launch.19 of these reports were from the consumer-authored letter, and were consumer complaints derived from the website described above.The remaining 15 reports were consistent with reporting rates prior to 2006. <table><tr><th>Year</th><th>Number of Spontaneous Reports</th><th>Reporting Rate per 100,000 years exposure*</th></tr><tr><td>1998</td><td>35</td><td>18.8</td></tr><tr><td>1999</td><td>38</td><td>8.6</td></tr><tr><td>2000</td><td>19</td><td>4.1</td></tr><tr><td>2001</td><td>14</td><td>2.8</td></tr><tr><td>2002</td><td>20</td><td>4.0</td></tr><tr><td>2003</td><td>14</td><td>2.7</td></tr><tr><td>2004</td><td>7</td><td>1.3</td></tr><tr><td>2005</td><td>5</td><td>0.9</td></tr><tr><td>2006</td><td>42</td><td>6.8</td></tr><tr><td>2007</td><td>17</td><td>2.6</td></tr><tr><td>2008†</td><td>7</td><td>1.8</td></tr><tr><td>Total</td><td>218</td><td>4.0</td></tr></table> <p>† Reports received through 18-Aug-2008 * Drug distribution data calculated through 31-Jul-2008</p> <p>A total of 218 spontaneous reports (16 serious, 7%) have been received with one or more of the ADRs (AEs) noted below. Seventy-eight reports were received from HCP's and 140 were from consumers.</p> <table><tr><th>MedDRA Preferred term</th><th>Number of ADRs* (Serious)</th></tr><tr><td>Depression</td><td>196 (12)</td></tr><tr><td>Depressed mood</td><td>14 (0)</td></tr><tr><td>Depressive symptom</td><td>8 (0)</td></tr><tr><td>Suicidal ideation</td><td>7 (2)</td></tr><tr><td>Depression suicidal</td><td>1 (0)</td></tr><tr><td>Major depression</td><td>1 (1)</td></tr><tr><td>Suicide attempt</td><td>1 (1)</td></tr><tr><td>Total Events</td><td>228 (16)</td></tr><tr><td>Total Reports</td><td>218 (16)</td></tr></table> <p>*A single report may include more than one ADR (AE), therefore the sum of the AEs can be greater than the total number of reports.</p>	Year	Number of Spontaneous Reports	Reporting Rate per 100,000 years exposure*	1998	35	18.8	1999	38	8.6	2000	19	4.1	2001	14	2.8	2002	20	4.0	2003	14	2.7	2004	7	1.3	2005	5	0.9	2006	42	6.8	2007	17	2.6	2008†	7	1.8	Total	218	4.0	MedDRA Preferred term	Number of ADRs* (Serious)	Depression	196 (12)	Depressed mood	14 (0)	Depressive symptom	8 (0)	Suicidal ideation	7 (2)	Depression suicidal	1 (0)	Major depression	1 (1)	Suicide attempt	1 (1)	Total Events	228 (16)	Total Reports	218 (16)
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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

40

Important Potential Risk Depressive Disorders	MedDRA Preferred Terms Depression
	<p>Of the 218 total reports received describing depression and depression related AEs, 48 reports described the patient as recovered/recovering from the depression, 46 reports described the patients as not recovered at the time of reporting and the outcome of depression and related depression events in the remaining 123 reports was unknown at the time of reporting. One fatal report was received from a sheriff's office and described a male who committed suicide by shooting. The medical examiner did not think this event was related to PROPECIA, in addition, the report provided insufficient information to allow for assessment.</p> <p>An analysis of serious depression reports (10) and serious and non-serious suicidality reports (9) are presented below. Of the 9 reports of suicidality, 6 were serious.</p> <p>A review of the 10 serious reports involving depression revealed 3 reports were received from an agency line listing and contained minimal information. Of the remaining 7 reports, one described a patient with a history of stress reaction which may have contributed to the event of depression. Three reports described patients who reported multiple AEs (e.g. seizures, muscle wasting, aggression, antisocial behavior, vision loss, and empty sella syndrome) indicating possibly other etiologies for the depression events confounding evaluation. Another report described a patient that experienced depression 1 year after initiating therapy with finasteride. Action taken with finasteride therapy was not provided which limits assessment. One report described a male who experienced depression, malaise and memory impairment 1 month after initiating treatment with finasteride. Treatment was discontinued and the patient recovered. The last report involved a patient who was rechallenged on therapy with finasteride and depression reoccurred; although causality cannot be ruled out in this case. Overall, these reports, including only 1 episode of a serious positive rechallenge, do not provide sufficient evidence of a causal association.</p> <p>There were a total of 9 suicidality reports (suicidal ideation, suicidal attempt, suicide), six of which were serious. There was one completed suicide. In the 9 suicidality reports, 4 contained insufficient information to allow a full evaluation. Three reports were confounded by concomitant medical conditions (chronic fatigue syndrome, thyroid disease, and concomitant medication consistent with a preexisting anxiety disorder). In the remaining two reports, the symptom of suicidality began after the patient discontinued finasteride.</p> <p>Reports of these events have been reviewed as part of the MAH's ongoing pharmacovigilance activities and reporting and the MAH has not observed an increase in frequency of events. This cumulative review has revealed no new safety information regarding depressive disorders.</p>

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11-Feb-2009

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1.6 Identified and Potential Interactions With Other Medicinal Products, Food, and Other Substances

No drug or food interactions of clinical importance for finasteride have been identified.

1.7 Epidemiology of the Indication(s) and Important Adverse Reactions**1.7.1 Incidence, Prevalence, Mortality, and Demographic Profile of the Target Population**

Indication/Target Population	Androgenic alopecia in males (male pattern hair loss)														
Incidence of Target Indication	No data available.														
Prevalence of Target Indication															
Rhodes T et al (1998) – United States [951]	<p>CLASSIFICATION: Men were classified as having no or little hair loss (Hamilton-Norwood types I, II), moderate hair loss (types III, III vertex, IV and V) or extensive hair loss (types VI and VII). Men were also categorized with predominantly frontal balding if they were classified as Type A variant, where the entire anterior border of the hairline lies high on the forehead and there is no balding vertex region.</p> <p>PREVALENCE BY AGE: The occurrence of MPHL was reported as follows for the age groups 18-29 years, 30-39 years, and 40-49 years, respectively. Little or no hair loss: Type I, 60%, 18%, 20%; Type II, 18%, 16%, 15%. Moderate hair loss: Type III, 3%, 6%, 4%; Type IIIv, 6%, 8%, 4%; Type IV, 3%, 7%, 11%; Type V, 0%, 5%, 8%. Extensive hair loss: Type VI, 1%, 12%, 11%; Type VII, 3%, 11%, 15%. Frontal hair loss: Type A variants, 6%, 17%, 11%. There was no apparent increasing trend with age for type A variants.</p> <p>TYPE A VARIANT: The proportion of Type A variants was reported as follows for the age groups 18-29 years, 30-39 years, and 40-49 years, respectively: Type IIa, 0%, 3%, 3%; Type IIIa, 1%, 2%, 0%; Type IVa, 0%, 0%, 2%; Type Va, 4%, 11%, 6%.</p>														
Norwood O (1975) – United States [136]	<p>Prevalence of male pattern hair loss</p> <table><tr><th>Age group</th><th>Moderate hair loss</th><th>Extensive Hair loss</th></tr><tr><td>18-29</td><td>11%</td><td>1%</td></tr><tr><td>30-39</td><td>35%</td><td>3%</td></tr><tr><td>40-49</td><td>46%</td><td>7%</td></tr></table> <p>Note: Moderate hair loss: Norwood- Hamilton patterns III, IIIv, IV, V; Extensive hair loss: Norwood- Hamilton patterns VI, VII</p>			Age group	Moderate hair loss	Extensive Hair loss	18-29	11%	1%	30-39	35%	3%	40-49	46%	7%
Age group	Moderate hair loss	Extensive Hair loss													
18-29	11%	1%													
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40-49	46%	7%													

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

42

Indication/Target Population	Androgenic alopecia in males (male pattern hair loss)		
Incidence of Target Indication	No data available.		
Hamilton JB (1951) – United States [172]	Prevalence of male pattern hair loss		
	Age group	Moderate hair loss	Extensive Hair loss
	15-29	23%	3%
	30-39	20%	22%
	40-49	25%	18%
	Note: Moderate hair loss: Norwood- Hamilton patterns III, IV, V; Extensive hair loss: Norwood- Hamilton patterns VI, VII		
Mortality in Target Indication	No data available.		
Potential Health Risk	No data available.		
Demographic Profile of Target Population	See prevalence of target indication section above.		

1.7.2 Important Co-Morbidity in the Target Population

Indication/Target Population	A number of comorbidities exist in this target population. However, given the mechanism of action of PROPECIA, the MAH did not identify any important co-morbidities that would alter the benefit/risk profile of PROPECIA in the target population.
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1.7.3 Epidemiology of the Condition in the Target Population when Unexposed to the Product

Identified Risk	Exposure during pregnancy– (potential for hypospadias in male fetus)
Incidence/Prevalence of Condition	
Bingol N and Wasserman E (1990) – Worldwide [569]	0.8-8 per 1000 live male births.
Abdullah NA (2007) – UK [1525]	Birth prevalence of hypospadias from 1993-2000: 3.1 per 1000 male live births.
Boisen KA (2005) – Denmark [1527]	Prevalence of hypospadias among live-born males from 1997-2004: 1.03% (95% CI: 0.51-1.83) or 5.25 per 1000 male live births (95% CI: 2.62-9.38/1000)
Pierik FH (2002) – Netherlands [1526]	26 per 10,000 live births
Kurahashi N (2004) – Japan [1523]	3.9 per 10,000 live births
Porter MP (2005) – United States (Washington State) [1524]	Birth prevalence of hypospadias for 2002: 5 per 1000 male births.

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

43

Gallentine (2001) – United States [1522]	Incidence of hypospadias overall and by racial group (1990-1998)	
	Overall	0.7%
	Race	
	White	0.8%
	Black	0.6%
	Asian	0.5%
	Native American	0.6%
	Unknown	0.6%
Mortality of Condition		No data available.

Identified Risk	Off-label use in women and adolescents
Incidence of Condition	No data available.
Prevalence of Condition	No data available.
Mortality of Condition	No data available.

Potential Risk	Persistence of erectile dysfunction		
Incidence of Condition	No data are available for the incidence of the <u>persistence</u> of erectile dysfunction; however several studies have estimated the incidence of erectile dysfunction using population-based data.		
Joahannes CB et al (2000) – United States [1214]	Massachusetts Male Aging Study (MMAS) N=847 men Follow up time: 8.8 years (rate per 1,000 person-years)		
	Group	Incidence rate	95% CI
	Overall	25.9	22.5-29.9
	Age group		
	40-49	12.4	9.0-16.9
	50-59	29.8	24.0-37.0
	60-69	46.4	36.9-58.4
Moreira, Jr, ED.et al (2003) -- Brazil [1532]	Population-based cohort study in Brazil (1998-2000) N=428 men Follow up time: 2.0 years (range: 1.7-2.3) (rate per 1,000 person-years)		
	Group	Incidence rate	95% CI
	Overall	65.6	49.6-85.2
	Age group (yrs)		
	40-49	33.3	NA
	50-59	53.7	
	60-69	189.5	
	Race		
	White	61.7	NA
	Black	60.7	
	Mixed	89.0	

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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

44

Potential Risk	Persistence of erectile dysfunction		
Schouten BWV et al (2005) – Netherlands [1553]	Krimpen Study N=781 men Follow up time: 2.1 years (range: 1.8-3.3) (rate per 1,000 person-years)		
	Group	Incidence rate	95% CI
	Overall	98.6	84.9-114.4
	Age group		
	50-59	76.5	61.4-95.3
	60-69	111.0	88.3-139.6
	70-78	205.4	130.9-322.2
Prevalence of Condition	Prevalence of mild, moderate/severe ED from epidemiological studies		
	Age range (years)	Mild	Moderate/Severe
Europe			
Denmark	18-88	--	5
Sweden	18-74	29	5
Norway	45+	--	8
Germany	30-80	23	19
Netherlands	40-79	--	13
France	18-70	28	11
France	18-69	28	19
Spain	25-70	16	3
USA	40-69	17	35
USA	40-79	--	12
USA	18-59	--	10
Australia	>40	--	23
Mortality of Condition	No data available.		

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

45

Potential Risk	Male infertility																																																																					
Incidence of Condition	No data available.																																																																					
Prevalence of Condition	<p>De Kretser et al (1997) – Worldwide [1518]</p> <p>One couple in 10 seeks medical help because of infertility. A 1982-85 study by the World Health Organization found that in 20% of cases the problem was predominantly male, in 38% the problem was predominantly female, in 27% abnormalities were found in both partners, and in the remaining 15% no clear-cut cause of infertility was identified. 10-20% of men with idiopathic azoospermia or severe oligospermia may harbor deletions in the distal section of the long arm of the Y chromosome. 1-2% of infertile males have congenital bilateral absence of the vas deferens.</p> <p>Bhasin S et al (1994) – Worldwide [1517]</p> <p>About 10% of males are infertile. Recognizable causes of the infertility are found in about 30 to 50% of cases. Only 10% to 20% of infertile men have treatable disorders such as genital tract obstruction, sperm autoimmunity, gonadotropin deficiency, coital disorders, and reversible toxin exposures.</p> <p>World Health Organization (1987) – Worldwide [1521]</p> <p>Laboratory and physical evaluation of 7273 couples from 33 centers who were infertile for at least 1 year.</p> <p>Distribution of diagnoses of male infertility</p> <table><tr><th>Diagnosis</th><th>Number of cases</th><th>% of cases</th></tr><tr><td>No demonstrable abnormality</td><td>3127</td><td>48.8</td></tr><tr><td>Varicocele</td><td>806</td><td>12.6</td></tr><tr><td>Idiopathic oligozoospermia</td><td>717</td><td>11.2</td></tr><tr><td>Accessory gland infection</td><td>441</td><td>6.9</td></tr><tr><td>Idiopathic teratozoospermia</td><td>376</td><td>5.9</td></tr><tr><td>Idiopathic asthenozoospermia</td><td>252</td><td>3.9</td></tr><tr><td>Isolated seminal plasma abnormalities</td><td>224</td><td>3.5</td></tr><tr><td>Suspected immunological factor</td><td>193</td><td>3.0</td></tr><tr><td>Congenital abnormalities</td><td>106</td><td>1.7</td></tr><tr><td>Systemic causes</td><td>91</td><td>1.4</td></tr><tr><td>Sexual inadequacy</td><td>81</td><td>1.3</td></tr><tr><td>Obstructive azoospermia</td><td>58</td><td>0.9</td></tr><tr><td>Idiopathic necrozoospermia</td><td>49</td><td>0.7</td></tr><tr><td>Ejaculatory inadequacy</td><td>42</td><td>0.6</td></tr><tr><td>Hyperprolactinaemia</td><td>39</td><td>0.6</td></tr><tr><td>Iatrogenic causes</td><td>36</td><td>0.6</td></tr><tr><td>Karyotype abnormality</td><td>31</td><td>0.5</td></tr><tr><td>Partial obstruction</td><td>6</td><td>0.1</td></tr><tr><td>Retrograde ejaculation</td><td>4</td><td>0.1</td></tr><tr><td>Immotile cilia syndrome</td><td>1</td><td>0.0</td></tr><tr><td>Pituitary lesion</td><td>1</td><td>0.0</td></tr><tr><td>Gonadotropin deficiency</td><td>1</td><td>0.0</td></tr></table>	Diagnosis	Number of cases	% of cases	No demonstrable abnormality	3127	48.8	Varicocele	806	12.6	Idiopathic oligozoospermia	717	11.2	Accessory gland infection	441	6.9	Idiopathic teratozoospermia	376	5.9	Idiopathic asthenozoospermia	252	3.9	Isolated seminal plasma abnormalities	224	3.5	Suspected immunological factor	193	3.0	Congenital abnormalities	106	1.7	Systemic causes	91	1.4	Sexual inadequacy	81	1.3	Obstructive azoospermia	58	0.9	Idiopathic necrozoospermia	49	0.7	Ejaculatory inadequacy	42	0.6	Hyperprolactinaemia	39	0.6	Iatrogenic causes	36	0.6	Karyotype abnormality	31	0.5	Partial obstruction	6	0.1	Retrograde ejaculation	4	0.1	Immotile cilia syndrome	1	0.0	Pituitary lesion	1	0.0	Gonadotropin deficiency	1	0.0
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11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

46

Potential Risk	Depressive disorders		
Incidence of Condition	Condition	General Population	Reference
	Depression ¹	2.8 per 1000 person yrs (total population, age-adj. rate)	Mattison 2005 (Lundby study, 1972-1997) [1558]
		<u>Age</u> <u>rate/1000 PY</u>	
		15-39 2.8	
		40-69 2.5	
70-99 3.6			
		7.0 per 1000 person yrs (total population)	Luijendijk 2008 [1559]
		14.7 per 1000 person yrs (males)	
Prevalence of Condition	Condition	General Population	Reference
	Mood Disorder ^{1,2}	28.0% (US, lifetime)	Kessler 2005 (NCS-R '01-'03) [1546]
		<u>Age</u> <u>%</u>	
		18-29 21.4	
		30-44 24.6	
		45-59 22.9	
	≥60 11.9		
	Major Depression ¹	2.9% (US males, past year)	Carpenter 2000 (NLAES, 1992) [1545]
		1.7% (US males, 15-39 yrs, past month)	Onyike 2003 (NHANES III '88-'94) [1555]
		6.8% (US males, current)	Strine 2008 [1554]
		11.1% (US males, lifetime)	
		6.7% (US, past year)	Kessler 2005b (NCS-R '01-'03) [1546]
		3.1-10.1% (Europe general population, past year)	Wittchen (2005) [1540]
		5.5% (Europe males, past year)	
		European males by Age, past year	
		<u>Age</u> <u>%</u>	
		18-34 6.0	
35-49 5.5			
50-65 4.8			

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11-Feb-2009

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

47

Potential Risk	Depressive disorders																																																																																																																											
	<table><tr><th>Condition</th><th colspan="2">General Population</th><th>Reference</th></tr><tr><td>Suicide Attempt</td><td colspan="2">1.5 / 1000</td><td rowspan="15">Doshi (2005) [1544]</td></tr><tr><td>OVERALL (ED visit)</td><td colspan="2"></td></tr><tr><td>By age (y)</td><td colspan="2"></td></tr><tr><td>0-14</td><td colspan="2">0.5</td></tr><tr><td>15-19</td><td colspan="2">3.3</td></tr><tr><td>20-29</td><td colspan="2">2.9</td></tr><tr><td>30-49</td><td colspan="2">2.0</td></tr><tr><td>50+</td><td colspan="2">0.5</td></tr><tr><td>By Sex</td><td colspan="2"></td></tr><tr><td>Male</td><td colspan="2">1.3</td></tr><tr><td>Female</td><td colspan="2">1.7</td></tr><tr><td>By Race</td><td colspan="2"></td></tr><tr><td>White</td><td colspan="2">1.5</td></tr><tr><td>Black</td><td colspan="2">1.9</td></tr><tr><td>Other</td><td colspan="2">NA</td></tr></table>	Condition	General Population		Reference	Suicide Attempt	1.5 / 1000		Doshi (2005) [1544]	OVERALL (ED visit)			By age (y)			0-14	0.5		15-19	3.3		20-29	2.9		30-49	2.0		50+	0.5		By Sex			Male	1.3		Female	1.7		By Race			White	1.5		Black	1.9		Other	NA																																																																										
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¹Based in DSM criteria

²Mood Disorder = major depression, dysthymia or bipolar disorder I or II

³Includes ideation, gestures, plans and attempts

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11-Feb-2009

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Potential Risk	Depressive disorders
Mortality of Condition	See data above for suicide completion.

1.8 Pharmacological Class Effects

PROPECIA (finasteride 1 mg) is the only Type 2 5 α -reductase inhibitor marketed for the treatment of male pattern hair loss.

Finasteride is a competitive and specific inhibitor of Type 2 5 α -reductase, an intracellular enzyme that converts the androgen testosterone to dihydrotestosterone (DHT). Two distinct isoenzymes are found in mice, rats, monkeys and humans: Type 1 and 2. Each of these isoenzymes is differentially expressed in tissues and developmental stages. In humans, Type 1 5 α -reductase is predominant in the sebaceous glands of most regions of the skin, including skin and liver. Type 1 5 α -reductase is responsible for approximately one-third of circulating DHT. The Type 2 5 α -reductase isoenzyme is primarily found in prostate, seminal vesicles epididymides, and hair follicles as well as liver, and is responsible for two-thirds of circulating DHT. In humans, the mechanism of action of finasteride is based on its preferential inhibition of the Type 2 isoenzyme. Using native tissue (scalp and prostate), *in vitro* binding studies examining the potential of finasteride to inhibit either isoenzyme revealed a 100-fold selectivity for the human type 2 5 α -reductase over the type 1 isoenzyme.

Inhibition of Type 2 5 α -reductase blocks the peripheral conversion of testosterone to DHT, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching 65% suppression within 24 hours of oral dosing with a 1 mg tablet. Mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared with baseline, but remained within the physiologic range.

In men with male pattern hair loss, the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with hairy scalp. Administration of finasteride decreases scalp and serum DHT concentrations in these men. By this mechanism, finasteride appears to interrupt a key factor in the development of male pattern hair loss in those patients genetically predisposed.

In the Phase III controlled studies in men with male pattern hair loss three clinical adverse experiences (decreased libido, erectile dysfunction and ejaculation disorder) were reported as drug related with an incidence greater than or equal to 1% of patients (see Table 9 below). In these same studies, the incidence of breast-related adverse experiences was low and balanced between the treatment groups (0.4% of finasteride patients and 0.4% of placebo patients).

Table 9

Drug-related Adverse Events for PROPECIA 1 mg in Year 1
Phase III Controlled Studies (087,089 and 092)
Incidence \geq 1%

Adverse Experience	Finasteride 1 mg N=945	Placebo N=934
Decreased Libido	1.8%	1.3%
Erectile Dysfunction	1.3 %	0.7%
Ejaculation Disorder	1.2%	0.7%
<i>(Decreased Volume of Ejaculate)</i>	<i>(0.8%)</i>	<i>(0.4%)</i>

In a clinical study with PROPECIA in men 18-41 years of age, designed to detect small changes in prostate size, 1 year of treatment with finasteride 1 mg resulted in a decrease in prostate volume of 0.7 cc (from 26.5 to 25.8 cc) associated with a decrease in serum prostate specific antigen (PSA) from 0.7 ng/mL to 0.5 ng/mL (See Annex 2). In clinical studies with PROSCAR (finasteride 5 mg) when used in men with benign prostatic hyperplasia (BPH), prostate volume is decreased by approximately 20% and serum PSA levels are decreased by approximately 50%. [1552]

AVODART™ (dutasteride 0.5 mg) is a competitive inhibitor of both type 1 and type 2 5 α -reductase isoenzymes and is marketed for the treatment of BPH. After 1 and 2 weeks of daily dosing with dutasteride 0.5 mg, median serum DHT concentrations were reduced by 85% and 90% respectively. In patients with BPH treated with dutasteride 0.5 mg/day for 4 years, the median decrease in serum DHT was 94% at 1 year. The median increase in testosterone was 19% at 1 year, with the mean and median levels remaining within the physiologic range.

The adverse experience profile for dutasteride is derived from data obtained from studies in men with BPH. In this population, the most common adverse reactions, reported in greater than or equal to 1% of patients treated with dutasteride and more commonly than in patients treated with placebo are impotence, decreased libido, ejaculation disorders and breast disorders (see Table 10 below).

Table 10

Adverse Reactions Reported in $\geq 1\%$ of Subjects Over a 24-Month Period and More Frequently in the Group Receiving AVODART™ Then the Placebo Group (Randomized, Double-Blind, Placebo-Controlled Studies Pooled) by Time of Onset

Adverse Reactions	Adverse Reaction Time on Onset				
		Month 0-6	Month 7-12	Month 13-18	Month 19-24
	AVODART™ (n)	(n= 2,167)	(n= 1,901)	(n= 1,725)	(n= 1,605)
	Placebo (n)	(n= 2,158)	(n= 1,922)	(n= 1,714)	(n= 1,555)
Impotence					
	AVODART™	4.7%	1.4%	1.0%	0.8%
	Placebo	1.7%	1.5%	0.5%	0.9%
Decreased Libido					
	AVODART™	3.0%	0.7%	0.3%	0.3%
	Placebo	1.4%	0.6%	0.2%	0.1%
Ejaculation disorders					
	AVODART™	1.4%	0.5%	0.5%	0.1%
	Placebo	0.5%	0.3%	0.1%	0.0%
Breast Disorders*					
	AVODART™	0.5%	0.8%	1.1%	0.6%
	Placebo	0.2%	0.3%	0.3%	0.1%

*Includes breast tenderness and breast enlargement.

Across 3 studies pooled, treatment with dutasteride for 12 months results in a mean percent change in prostate volume of -24.7%. Dutasteride reduces serum PSA concentrations by approximately 50% following 6, 12 and 24 months of treatment. [1551]

1.9 Additional Requirements

1.9.1 Potential for Overdose

Postmarketing Reports of Overdose

The MAH has received postmarketing reports of PROPECIA overdose, defined as ingestion of at least one dose exceeding that recommended in the product label for the indication of androgenetic hair loss. As of 18-Aug-2008, the company pharmacovigilance database contains 130 reports where at least one dose of PROPECIA in excess of 1 mg QD was ingested. [These 130 reports also include reports of doses in excess of 0.2 mg QD from Japan, the only country in which PROPECIA 0.2 mg is an approved dose], 20 of these reports are HCP reports, and 110 are consumer reports. In 57 reports, the overdose is consumed by an adult; in 31 reports by a child under the age of 18; and 42 reports do not specify patient age.

An additional 43 reports were identified which were coded as overdose, but the dose described falls within that recommended in the product label; 35 of these reports are in children under 18.

The adult experience is summarized below; reports of pediatric overdose are discussed in Section 3.2 Potential for Medication Errors.

Of the 57 reports of adult overdose, a majority involve ingestion of 2 or 3 milligrams of PROPECIA either as a single event (accidental or in order to make up a missed dose), or on a more chronic basis in an attempt by the patient to increase efficacy. Eighteen of the 57 reports describe adverse drug reactions in response to the PROPECIA overdose; the remaining 39 reports indicate no adverse reaction other than the overdose itself. The most frequently reported ADRs are hypertrichosis (3 reports), testicular/groin/penile pain (4 reports), gynecomastia (2 reports), erectile dysfunction (2 reports), and gastritis (2 reports). No deaths are reported. Six serious ADRs are described besides the overdoses themselves: these are osteonecrosis of the femoral head (1 report), groin pain (1 report), penile pain (1 report), gynecomastia (1 report), hypertrichosis (1 report), and anger (1 report). There was no relationship between higher doses of PROPECIA and frequency or seriousness of ADRs.

Of the 42 reports that do not specify patient age, 38 involve ingestion of 2 or 3 milligrams of PROPECIA either as a single event (accidental or in order to make up a missed dose), or on a more chronic basis in an attempt by the patient to increase efficacy. A total of 3 adverse drug reactions are described in these 42 reports; impotence (1 report); erythema of the face (1 report); and multiple congenital anomalies in an infant born to a mother exposed to the semen of her partner, which is discussed in Section 1.5.2 Details of Important Identified and Important Potential Risks.

In summary, the MAH has received 130 reports of PROPECIA overdose. In adults, the majority of overdoses involve ingestion of 2 to 3 mg of PROPECIA, either as a single event or on a chronic basis. The majority of adults exposed to PROPECIA overdose do not experience ADRs. The most frequently reported ADRs reported in these patients are hypertrichosis (3 reports), testicular/groin/penile pain (4 reports), gynecomastia (2 reports), erectile dysfunction (2 reports), and gastritis/stomach upset (2 reports). Serious events included osteonecrosis of the femoral head (1 report), groin pain (1 report), penile pain (1 report), gynecomastia (1 report), hypertrichosis (1 report), and anger (1 report). Testicular pain, gynecomastia, and erectile dysfunction are all listed adverse reactions for PROPECIA.

1.9.2 Potential for Transmission of Infectious Agents

Finasteride is an oral product that is manufactured in accordance with current Good Manufacturing Practices (cGMPs). All raw materials and the drug substance used in the manufacture of the drug product are sourced from suppliers that guarantee the absence of Bovine Spongiform Encephalopathy (BSE) and/or Transmissible Spongiform Encephalopathy (TSE). Microbial testing is performed to demonstrate the absence of objectionable organisms.

1.9.3 Potential for Misuse for Illegal Purposes**Postmarketing Reports**

The MAH has received no reports of PROPECIA misuse for illegal purposes from market introduction to 18-Aug-2008. The company pharmacovigilance database contains a single report of drug dependence (physical and psychological); one report of pharmaceutical product counterfeit; and nine reports of intentional misuse, which include reports of patient-initiated dose adjustments to enhance therapeutic effect or decrease side effects, tablet splitting, and concomitant use of recreational drugs.

The MAH is aware of literature describing the potential use of finasteride as a masking agent in "doping" (use of illegal steroids in sports) [1550]. However, the MAH has not identified any reports of this particular use in postmarketing data.

Postmarketing data do not suggest any pattern of misuse of PROPECIA for illegal purposes.

1.9.4 Potential for Off-Label Use

Off-label use by healthcare professionals is a possibility with any marketed product. Although the extent of off-label use is not known, off-label use has been documented in the company pharmacovigilance database. Off-label Use in Women and Adolescents is discussed in Section 1.5.2 Details of Important Identified and Important Potential Risks. A postmarketing review of off-label use in males and gender not specified is presented below.

The Merck Worldwide Adverse Experience System (WAES) database was searched from market introduction (11-Sep-1997) to 18-Aug-2008 for reports with the following MedDRA preferred terms: 'Off-label use', 'Drug ineffective for unapproved indication', 'Therapeutic product ineffective for unapproved indication' and the lower level terms: 'Drug use for unapproved indication', 'Drug use via unapproved administration route', and 'Intentional use for unlabeled indication' in the male and "gender not identified" population.

In addition to the identified reports with terms as above, reports involving off-label indications for finasteride 0.2 mg and 1 mg tablet (PROPECIA) were reviewed. Reports where indication was not reported were not included in this review. A small number of off-label indications were identified. Most commonly, finasteride 0.2 mg and 1 mg tablet (PROPECIA) has been used off-label for conditions related to hair and scalp disorders (e.g., hairiness and "prophylaxis to prevent hair loss") and hormonal conditions. Most of the remaining off-label indications were related to prostate signs/symptoms which may be due to the approved indication for finasteride 5 mg tablet (PROSCAR) for the treatment and control of benign prostatic hyperplasia (BPH).

Table 11 and Table 12 below outline the twenty most frequent ADRs and the most frequent serious ADRs in these reports of off-label use.

Table 11

Off-Label Use in Men and Gender Not Specified Populations
Twenty Most Frequent Reported ADRs

ADR	N
Alopecia	21
Libido decreased	11
Drug ineffective	10
Erectile dysfunction	10
Off-label use	9
Sexual dysfunction	8
Gynaecomastia	7
Dizziness	6
Drug administration error	6
Pruritus	6
Therapeutic response unexpected	6
No ADR	6
Rash	5
Therapeutic response decreased	5
Semen volume decreased	5
Asthenia	4
Testicular pain	4
Headache	4
Acne	3
Breast tenderness	3
Other	136
Total	275

Table 12
Off-Label Use in Men and Gender Not Specified Populations
Most Frequent Serious ADRs

ADR	N
Gynaecomastia	2
Arthropathy	1
Asthenia	1
Incorrect dose administered	1
Myocardial infarction	1
Penile size reduced	1
Psychotic disorder	1
Sperm count decreased	1
Weight decreased	1
Testis cancer	1
Semen volume decreased	1
Post procedural complication	1
Overdose	1
Muscle twitching	1
Hypotension	1
Cerebrovascular accident	1
Other	0
Total	17

The majority of AE reports involving use of finasteride in the off-label use population reflect the AE profile seen in patients in whom the drug is used per indication. The serious events described in Table 12 were mostly single cases and no obvious pattern was identified indicating a safety signal.

No new safety issues associated with off-label use were identified during this reporting period for finasteride (PROPECIA).

1.9.5 Potential for Off-Label-Pediatric Use

Off-label Use in Adolescents 12-17 years is discussed in Section 1.5.2 Details of Important Identified and Important Potential Risks. The EUSPC states: PROPECIA should not be used in children. There are no data demonstrating efficacy or safety of finasteride in children under the age of 18.

1.10 Summary—Ongoing Safety Concerns

Important Identified Risks	Exposure during Pregnancy Off-label use in Women and Adolescents
Important Potential Risks	Persistence of Erectile Dysfunction Male Infertility Depressive Disorders
Important Missing Information	Not Applicable

2. Pharmacovigilance Plan**2.1 Routine Pharmacovigilance Practices**

All applicable laws and regulations concerning the reporting of ADR information are adhered to in order to ensure compliance in every respect with worldwide reporting requirements. It is the policy of Merck, Sharpe, and Dohme that the reporting of ADRs to all appropriate regulatory agencies is accomplished in accordance with the relevant legal requirements and appropriate international declarations and protocols.

A detailed description of pharmacovigilance practices is provided in the Detailed Description of the Pharmacovigilance System document located in Module 1.8.1.1. A detailed description of pharmacovigilance practices includes the following:

- Description of the pharmacovigilance database
- Pharmacovigilance standard operating procedures documented in writing
- Qualified person(s) regarding availability and means for notification of ADRs
- Links with other organizations

2.2 Summary of Safety Concern and Planned Pharmacovigilance Actions

Safety Concern	Planned Action(s)
Important Identified Risks Exposure during Pregnancy	Routine pharmacovigilance
Off-label use in Women and Adolescents	Routine pharmacovigilance
Important Potential Risks Persistence of Erectile Dysfunction	Routine pharmacovigilance
Male Infertility	Routine pharmacovigilance
Depressive Disorders	Routine pharmacovigilance
Important Missing Information Not Applicable	Not applicable

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

56

2.3 Detailed Action Plan for Specific Safety Concerns

Safety Concern	Exposure during pregnancy
Identified or potential risk or missing information	Important identified risk
Action(s) proposed	Routine pharmacovigilance
Objective of proposed action(s)	To identify, evaluate, and monitor postmarketing reports of pregnancy in women exposed to finasteride via oral, semen, dermal, or inhalation routes. To further describe and characterize potential sequelae, if any, of finasteride in pregnant patients and/or the fetus/newborn.
Rationale for proposed action(s)	The proposed actions will allow Merck to gather information to continue to evaluate and characterize the effects, if any, of finasteride on pregnant patients and/or the fetus/newborn.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Upon review of the data, appropriate measures will be taken if new information alters the benefit/risk profile of finasteride.
Milestones for evaluation and reporting including justification for choice of milestones	Pregnancy exposures to finasteride will be reviewed and included in the standard <i>Pregnancy</i> section of the annual Periodic Safety Update Report.
Titles of protocols	N/A

Safety Concern	Off-label use in women and adolescents
Identified or potential risk or missing information	Important identified risk
Action(s) proposed	<p>Routine pharmacovigilance</p> <p>Recently the MAH included a cross reference from section 4.3 of the EU SPC to section 5.1 which includes results from a study in postmenopausal women with androgenic alopecia who were treated with finasteride 1 mg for 12 months and in which efficacy compared to placebo was not demonstrated. In addition, the MAH strengthened the warning against use in children in section 4.4, warnings and precautions to indicate that this warning is based on lack of efficacy and safety data in children and adolescents under the age of 18. These EU SPC label changes are listed below (in bold).</p> <p>Section 4.3 Contra-indications</p> <p>Contraindicated in women: see 4.6 Pregnancy and lactation and 5.1 Pharmacodynamic properties.</p> <p>Hypersensitivity to finasteride or to any of the excipients.</p> <p>Section 4.4 Special warnings and special precautions for use</p> <p>PROPECIA should not be used in children. There are no data demonstrating efficacy or safety of finasteride in children under the age of 18.</p>

BW4172.doc VERSION 4.2 APPROVED

11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

57

Objective of proposed action(s)	To identify, evaluate, and monitor postmarketing reports of off-label use of finasteride in women and adolescents
Rationale for proposed action(s)	The proposed actions will allow Merck to gather information in order to continue to evaluate and characterize the off-label use of finasteride in women and adolescents
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Upon review of the data, appropriate measures will be taken if new information alters the benefit/risk profile of finasteride.
Milestones for evaluation and reporting including justification for choice of milestones	Postmarketing reports of off-label use with finasteride in women and adolescents will be reviewed and included in the standard <i>Off-label Use</i> section of the annual Periodic Safety Update Report.
Titles of protocols	N/A

Safety Concern	Persistence of erectile dysfunction
Identified or potential risk or missing information	Important potential risk
Action(s) proposed	Routine pharmacovigilance
Objective of proposed action(s)	To identify, evaluate, and monitor postmarketing reports of persistent erectile dysfunction in patients taking finasteride.
Rationale for proposed action(s)	The proposed actions will allow Merck to gather information in order to continue to evaluate and characterize persistent erectile dysfunction in patients on finasteride.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Upon review of the data, appropriate measures will be taken if new information alters the benefit/risk profile of finasteride.
Milestones for evaluation and reporting including justification for choice of milestones	The MAH will regularly review and evaluate postmarketing reports of erectile dysfunction with a focus on persistence of the AE in the annual Periodic Safety Update Report for 2 years.
Titles of protocols	N/A

Safety Concern	Male Infertility
Identified or potential risk or missing information	Important potential risk
Action(s) proposed	Routine pharmacovigilance
Objective of proposed action(s)	To identify, evaluate, and monitor reports of male infertility in men taking finasteride.
Rationale for proposed action(s)	The proposed actions will allow Merck to gather information to continue to evaluate and characterize male infertility in patients on finasteride.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Upon review of the data, appropriate measures will be taken if new information alters the benefit/risk profile of finasteride.
Milestones for evaluation and reporting including justification for choice of milestones	The MAH will regularly review and evaluate postmarketing reports of male infertility in the annual Periodic Safety Update Report for 2 years.
Titles of protocols	N/A

BW4172.doc VERSION 4.2 APPROVED

11-Feb-2009

Restricted Confidential – Limited Access

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

58

Safety Concern	Depressive Disorders
Identified or potential risk or missing information	Important potential risk
Action(s) proposed	Routine pharmacovigilance
Objective of proposed action(s)	To identify, evaluate, and monitor postmarketing reports of depression and/or depressive disorders in patients taking finasteride.
Rationale for proposed action(s)	The proposed actions will allow Merck to gather information to continue to evaluate and characterize depression and/or depressive disorders in patients on finasteride.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Upon review of the data, appropriate measures will be taken if new information alters the benefit/risk profile of finasteride.
Milestones for evaluation and reporting including justification for choice of milestones	The MAH will regularly review and evaluate postmarketing reports of depressive disorders in the annual Periodic Safety Update Report for 2 years.
Titles of protocols	N/A

2.4 Overview of Study Protocols for the Pharmacovigilance Plan

None

2.5 Risk Management Plan Updates

Not applicable; first Risk Management Plan submission

2.6 Summary of Outstanding Actions, Including Milestones

None

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

59

PART II

3. Evaluation of the Need for a Risk Minimization Plan

3.1 Summary Table for Important Safety Concerns

Safety Concern	Routine Risk Minimisation Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification
Concern: Important identified risks (List) Exposure during Pregnancy	Yes	<p>Routine pharmacovigilance</p> <p>Labeling EUSPC Section 4.3 Contraindications Contra-indicated in women</p> <p>Section 4.6 Pregnancy <i>Pregnancy:</i> PROPECIA is contraindicated for use in women due to the risk in pregnancy. Because of the ability of finasteride to inhibit conversion of testosterone to dihydrotestosterone (DHT) PROPECIA may cause abnormalities of the external genitalia of a male fetus when administered to a pregnant woman</p> <p>Section 6.6 Instructions for use and handling Crushed or broken tablets of PROPECIA should not be handled by women when they are or may potentially be pregnant because of the possibility of absorption of finasteride and subsequent potential risk to a male fetus (see 4.6 Pregnancy and lactation). PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.</p> <p>The actions described in the pharmacovigilance plan are deemed appropriate to address the risk of exposure during pregnancy.</p>
Off-label use in Women and Adolescents	Yes	<p>Routine pharmacovigilance</p> <p>Labeling EUSPC Section 4.3 Contraindications Contra-indicated in women: see 4.6 Pregnancy and lactation and 5.1 Pharmacodynamic properties</p>

BW4172.doc VERSION 4.2 APPROVED

11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

60

Safety Concern	Routine Risk Minimisation Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification
		<p>Section 4.4 Special warnings and special precautions for use PROPECIA should not be used in children. There are no data demonstrating efficacy or safety of finasteride in children under the age of 18.</p> <p>Section 4.6 Pregnancy <i>Pregnancy:</i> PROPECIA is contraindicated for use in women due to the risk in pregnancy. Because of the ability of finasteride to inhibit conversion of testosterone to dihydrotestosterone (DHT) PROPECIA may cause abnormalities of the external genitalia of a male fetus when administered to a pregnant woman</p> <p>5.1 Pharmacodynamic properties <i>Studies in women:</i> Lack of efficacy was demonstrated in postmenopausal women with androgenetic alopecia who were treated with finasteride 1 mg for 12 months.</p> <p>Section 6.6 Instructions for use and handling Crushed or broken tablets of PROPECIA should not be handled by women when they are or may potentially be pregnant because of the possibility of absorption of finasteride and subsequent potential risk to a male fetus (see 4.6 Pregnancy and lactation). PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.</p> <p>The actions described in the pharmacovigilance plan are deemed appropriate to address the risk of off-label use in women and adolescents.</p>
Important potential risks (List) Persistence of Erectile Dysfunction	Yes	<p>Routine pharmacovigilance Labeling EUSPC</p> <p>Section 4.8 Undesirable effects The adverse reactions during clinical trials and/or post-marketing use are listed in the</p>

BW4172.doc VERSION 4.2 APPROVED

11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

61

Safety Concern	Routine Risk Minimisation Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification		
		<p>table below.</p> <p>Frequency of adverse reactions is determined as follows: Very Common ($\geq 1/10$); Common ($\geq 1/100$, $< 1/10$); Uncommon ($\geq 1/1,000$, $< 1/100$); Rare ($\geq 1/10,000$, $< 1/1,000$); Very rare ($< 1/10,000$); not known (cannot be estimated from the available data). The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports.</p> <table><tr><td>Reproductive system and breast disorders:</td><td><i>Uncommon*</i>: Erectile dysfunction, ejaculation disorder (including decreased volume of ejaculate). <i>Not known</i>: Breast tenderness and enlargement, Testicular pain, infertility**. **See section 4.4.</td></tr></table> <p>*Incidences presented as difference from placebo in clinical studies at Month 12.</p> <p>Drug-related sexual undesirable effects were more common in the finasteride-treated men than the placebo-treated men, with frequencies during the first 12 months of 3.8% vs 2.1%, respectively. The incidence of these effects decreased to 0.6% in finasteride-treated men over the following four years. Approximately 1% of men in each treatment group discontinued due to drug related sexual adverse experiences in the first 12 months, and the incidence declined thereafter.</p> <p>Persistence of erectile dysfunction after discontinuation of treatment with PROPECIA has been reported in post-marketing use.</p>	Reproductive system and breast disorders:	<i>Uncommon*</i> : Erectile dysfunction, ejaculation disorder (including decreased volume of ejaculate). <i>Not known</i> : Breast tenderness and enlargement, Testicular pain, infertility**. **See section 4.4.
Reproductive system and breast disorders:	<i>Uncommon*</i> : Erectile dysfunction, ejaculation disorder (including decreased volume of ejaculate). <i>Not known</i> : Breast tenderness and enlargement, Testicular pain, infertility**. **See section 4.4.			

BW4172.doc VERSION 4.2 APPROVED

11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

62

Safety Concern	Routine Risk Minimisation Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification
		The actions described in the pharmacovigilance plan are deemed appropriate to address the risk of persistent erectile dysfunction.
Male infertility	Yes	<p>Routine pharmacovigilance</p> <p>Labeling EUSPC</p> <p>Section 4.4: Special warnings and special precautions for use Long-term data on fertility in humans are lacking, and specific studies in subfertile men have not been conducted. The male patients who were planning to father a child were initially excluded from clinical trials. Although, animal studies did not show relevant negative effects on fertility, spontaneous reports of infertility and /or poor seminal quality were received post-marketing. In some of these reports, patients had other risk factors that might have contributed to infertility. Normalisation or improvement of seminal quality has been reported after discontinuation of finasteride.</p> <p>Section 4.8 Undesirable effects The adverse reactions during clinical trials and/or post-marketing use are listed in the table below. Frequency of adverse reactions is determined as follows: Very Common ($\geq 1/10$); Common ($\geq 1/100$, $< 1/10$); Uncommon ($\geq 1/1,000$, $< 1/100$); Rare ($\geq 1/10,000$, $< 1/1,000$); Very rare ($< 1/10,000$); not known (cannot be estimated from the available data). The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports.</p>

BW4172.doc VERSION 4.2 APPROVED

11-Feb-2009


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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

63

Safety Concern	Routine Risk Minimisation Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification
		<div data-bbox="959 384 1338 884"> <div data-bbox="959 384 1138 884"> Reproductive system and breast disorders: </div> <div data-bbox="1138 384 1338 884"> <i>Uncommon*</i>: Erectile dysfunction, ejaculation disorder (including decreased volume of ejaculate). <i>Not known</i>: Breast tenderness and enlargement, Testicular pain, infertility**. **See section 4.4. </div> </div> <p data-bbox="914 884 1338 968">*Incidences presented as difference from placebo in clinical studies at Month 12.</p> <p data-bbox="914 968 1338 1136">The actions described in the pharmacovigilance plan are deemed appropriate to address the risk of persistent erectile dysfunction.</p>
Depression	Yes	<p data-bbox="914 1136 1338 1178">Routine pharmacovigilance</p> <p data-bbox="914 1178 1338 1791">The proposed actions will allow Merck to gather information to continue to evaluate and characterize depression and/or depressive disorders in patients on finasteride. Reports of these events have been reviewed as part of ongoing pharmacovigilance and the MAH has not observed an increase in frequency of events. The estimated reporting rate of depressive disorders is 4.0 events per 100,000 patient-years of exposure. While there is a paucity of incidence data on depression and depressive-related disorders in the general population, estimates of the incidence of depressive disorders have been reported to range from 2.8 to 14.7 per 1000 person years [1558; 1559]. In addition, the World Health Organization has reported a global age-adjusted incidence rate (per 100,000 population) of 3199 in males (range: 2028-4294 per 100,000 population) [1561].</p>

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11-Feb-2009

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

64

Safety Concern	Routine Risk Minimisation Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification
		While these rates are not directly comparable, it does give some context as to the low occurrence of depressive disorders observed in patients on PROPECIA. Our cumulative review (data presented in Section 1.5.2 <u>Details of Important Identified and Important Potential Risks</u>) has revealed no new safety information regarding depressive disorders. The MAH will continue to monitor reported events of depression.
Important mission information (List)	Not applicable	Not applicable

3.2 Potential for Medication Errors

Finasteride tablets, 1 mg are conventional, embossed film-coated tablets containing 1 mg of finasteride in a total tablet weight of 154 mg. The film-coat includes red and yellow iron oxide pigments to give a tan colour and the tablet image is a distinctive octagonal shape. Standard procedures were followed in developing the trade name PROPECIA, which involved extensive consideration of similar nomenclature, in order to minimize the risk of confusion at the time of prescribing or dispensing the drug. In addition, standard procedures were followed in developing the tablet appearance (size, shape, color) to minimize the risk of confusion with other medications.

Postmarketing Reports

The MAH has received a total of 877 medication error reports from HCPs, including regulatory agencies, and consumers from market introduction through 18-Aug-2008. Ninety-seven of these reports were in pediatric patients. All pediatric overdose reports have been included in this analysis of medication error, because PROPECIA is not indicated in nor prescribed to children, all reports of pediatric overdose are considered medication error, and have been combined with reports of pediatric medication error for the purpose of this discussion.

There were 780 reports of medication error in adults. The medication errors described in these reports are drug administration error (433); accidental exposure (126); drug exposure during pregnancy (103); wrong technique in drug usage process (84); inappropriate schedule of drug administration (61); overdose (39); medication error (36); and accidental overdose (32). The most commonly reported drug administration errors include splitting tablets, missed dose, accidental ingestion of more than one tablet per day, intentional ingestion of more than one tablet per day in an attempt to enhance therapeutic effect, dispensing of PROSCAR (5 mg) instead of PROPECIA (1 mg), administration to a female (discussed in Section 1.5.2 Details of Important Identified and Important Potential Risks: Off-label use), product confusion (use of PROPECIA instead of another product such as vitamins or nonsteroidal anti-inflammatory drugs, and, reports of exposure in pregnancy are discussed in Section 1.5.2 Important Identified Risks:

BW4172.doc VERSION 4.2 APPROVED

11-Feb-2009

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Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

65

Exposure During Pregnancy. Reports of PROPECIA overdose are discussed in Section 1.9.1 Potential for Overdose.

Adult Medication Error:

Of the 780 medication error reports in adults, 48 described an overdose (discussed in Section 1.9.1 Potential for Overdose), and 204 described no ADRs beside the medication error itself. The following tables outline the twenty most frequent ADRs and the twenty most frequent serious ADRs in the remaining 528 patients:

Medication Error: 20 Most Frequent ADRs	N	Medication Error: 20 Most Frequent Serious ADRs	N
Drug administration error	282	Abortion spontaneous	21
Accidental exposure	110	Abortion induced	5
Drug exposure during pregnancy	100	Hypospadias	4
Alopecia	67	Cardiac disorder	2
Wrong technique in drug usage process	66	Genitalia external ambiguous	2
Inappropriate schedule of drug administration	41	Cryptorchism	2
No ADR	38	Cerebrovascular accident	2
Drug ineffective	34	Pharmaceutical product complaint	2
Libido decreased	33	Premature baby	2
Erectile dysfunction	24	Hypersensitivity	2
Abortion spontaneous	21	Abnormal faeces	1
Medication error	16	Alopecia	1
Rash	15	Astrocytoma	1
Pruritus	13	Blood creatinine increased	1
Therapeutic response decreased	13	Breast cancer	1
Breast enlargement	12	Breech presentation	1
Nausea	11	Face oedema	1
Semen volume decreased	11	Epistaxis	1
Headache	10	Eclampsia	1
Hair texture abnormal	9	Death	1
Other	582	Other	53
Total	1508	Total	107

Finasteride 1 mg is contraindicated for use in women in the EU; reports of abortion, hypospadias, premature baby, external genitalia, and cryptorchism are discussed in Section 1.5.2 Details of Important Identified and Important Potential Risks. The remainder of ADRs occurring in conjunction with medication error do not show any pattern, and do not provide any new safety information.

Pediatric Medication Error:

There were a combined total of 97 reports of pediatric overdose and pediatric medical error. The medication errors described in these were accidental exposure (51); accidental drug intake by child (37); accidental overdose (35); overdose (23); drug administration

error (7); and medication error (2). The most frequent ADRs (serious and nonserious) are outlined in Table 13.

Table 13

Pediatric Medication Error: 20 Most Frequent ADRs

ADR	N
No ADR	73
Accidental exposure	51
Accidental drug intake by child	37
Accidental overdose	35
Overdose	23
Drug administration error	7
Medication error	2
Abdominal discomfort	1
Testicular pain	1
Breast enlargement	1
Drug dispensing error	1
Papilloedema	1
Retching	1
Erythema	1
Intentional drug misuse	1
Other	0
Total	236

There were 8 ADRs reported in the pediatric population besides the medication error and/or overdose itself. Two are labeled (testicular pain, breast enlargement). None were serious.

Review of cumulative postmarketing data on medication error in both adult and pediatric populations reveals no new information that would suggest a unique safety concern with regard to medication errors.

4. Risk Minimization Plan

The available safety information from the clinical and post-marketing environments, in addition to ongoing pharmacovigilance activities do not indicate additional risk minimization actions are needed. The MAH proposes that routine risk minimization is sufficient.

Finasteride—Male Pattern Hair Loss
Risk Management Plan Version Number 1.0

67

5. Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimization Activities (routine and additional)
<u>Important Identified Risks</u>		Labeling-EU SPC
Exposure during Pregnancy	Routine Pharmacovigilance	Section 4.3 Contraindications Section 4.6 Pregnancy and lactation Section 6.6 Instructions for use and handling
Off-label use in Women and Adolescents	Routine Pharmacovigilance	Section 4.3 Contraindications Section 4.4 Special warnings and special precautions for use Section 4.6 Pregnancy and lactation Section 5.1 Pharmacodynamic properties Section 6.6 Instructions for use and handling
<u>Important Potential Risks</u>		Labeling – EU SPC
Persistence of Erectile Dysfunction	Routine Pharmacovigilance	Section 4.8 Undesirable effects
Male Infertility	Routine Pharmacovigilance	Section 4.4 Special warnings and special precautions for use Section 4.8 Undesirable effects
Depressive Disorders	Routine Pharmacovigilance	
<u>Important Missing Information</u>		
Not Applicable		

6. Contact Person for this RMP – Provided as a separate component.

BW4172.doc VERSION 4.2 APPROVED

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11-Feb-2009

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69

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Risk Management Plan Version Number 1.0

70

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