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27 World's Fair Drive
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June 8, 2022

RE: Docket No. FDA-2017-P-5787

Dear Dr. Santmann:

This letter responds to your citizen petition received on September 18, 2017 (Petition), and the two supplements received on December 1, 2020 (Supplements), submitted on behalf of the Post-Finasteride Syndrome Foundation (PFSF). In the Petition, you request that the Food and Drug Administration (FDA, the Agency, or we) require the immediate removal of Propecia (new drug application (NDA) 020788), 1 milligram (mg), oral tablets, and all generic versions of Propecia, 1 mg, for androgenic alopecia[1] from the market. Alternatively, you request that FDA revise the labels for Propecia and generic finasteride to warn of serious and severe risks, amend certain language, and require a Risk Evaluation and Mitigation Strategy (REMS). Finally, you request that FDA revise the labeling for Proscar (NDA 020180), 5 mg, oral tablets, and generic versions of Proscar, to indicate that the tablet should not be split into quarters for the treatment of androgenic alopecia and to delete certain language from the ADVERSE REACTIONS section (Petition at 1). Your December 1, 2020 Supplements provide additional justification for your requests set forth in the Petition.

FDA has carefully considered the information submitted in the Petition and Supplements and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, the Petition is denied in part and granted in part.

I. FINASTERIDE (PROPECIA AND PROSCAR)

Finasteride is a 5α-reductase inhibitor that reduces the conversion of testosterone to 5α-dihydrotestosterone. Two finasteride products are currently available in the United States. FDA's Division of Urology, Obstetrics, and Gynecology (formerly the Division of Bone, Reproductive, and Urologic Products) approved finasteride, 5 mg (Proscar, NDA 020180), on June 19, 1992, for the treatment of symptomatic benign prostatic hyperplasia (BPH). The Division of Dermatology and Dentistry (formerly the Division of Dermatology and Dental Products) approved finasteride, 1 mg (Propecia, NDA 020788), on December 19, 1997, for the treatment of male pattern hair loss (androgenic alopecia) in men. Generic versions are available for both products.

[1] Male pattern hair loss is also referred to, interchangeably, as male pattern baldness (MPB) and androgenic alopecia. All three terms refer to the condition with genetic disposition whereby there is a gradual conversion of terminal hairs into indeterminate, and finally into vellus, hairs in susceptible scalp areas.

A. Propecia (NDA 020788)

On December 20, 1996, Merck Research Laboratories (Merck)[2] submitted a 505(b)(2) NDA for Propecia (finasteride) tablet, 1 mg, for male pattern baldness (MPB) in men.[3] Finasteride is a 5α-reductase inhibitor known by the chemical name, *N*-(1,1-Dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide.

MPB is considered a physiological condition that differs in degree and onset. Furthermore, the occurrence of MPB in younger men is associated with psychosocial disturbance. It is generally believed that MPB is mediated by androgenic action. MPB is characterized by an androgen-mediated decrease in the ratio of anagen to telogen hair follicles and an increase in the proportion of vellus, or vellus-like, miniaturized follicles as compared with terminal follicles. Thus, inhibiting the androgen-mediated effects on hair follicles was a goal for treatment.

5α-reductase inhibitors are a class of drug used to treat, among other things, MPB. 5α-reductase converts testosterone into an active metabolite, dihydrotestosterone (DHT). There are two 5α-reductase isozymes (Type I and Type II). Studies have shown that the Type II isozyme is present in the scalp hair follicles while the Type I isozyme is present in the sebaceous glands in the scalp skin. Since finasteride is a selective Type II 5α-reductase inhibitor and specifically inhibits DHT-mediated effects on target tissues without affecting testosterone-mediated effects, finasteride was studied in the treatment of MPB.[4]

Two phase 3 clinical trials performed as double-blind, placebo-controlled, randomized, parallel-group, multicenter studies on hair loss (087 and 089) were the basis for the approval of NDA 020788.[5] Significant efficacy was evident based on both patient self-assessment and investigator assessment within 3 months of beginning treatment.[6] The studies established the efficacy of finasteride in men ages 18-41 with mild to moderate degrees of androgenic alopecia.[7]

Generally, the safety studies showed that treatment with Propecia was well-tolerated and there was a low incidence of drug-related adverse events.[8] The safety studies for Propecia showed that the most common drug-related adverse reactions were related to sexual function (decreased libido, erectile or ejaculatory dysfunction) and breast symptoms, but the studies also showed that the adverse events might resolve off therapy or even when the patient continues therapy.[9]

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[2] The Petition requests that FDA take certain actions with respect to Propecia, previously owned by Merck. On December 4, 2020, FDA received a notice of transfer of ownership of the Propecia NDA (020788) from Merck Sharp & Dohme Corp, a Subsidiary of Merck & Co, Inc., to Organon LLC (Organon). Therefore, we have addressed all labeling change requirements under 21 U.S.C. §505(o)(4) regarding Propecia to Organon.
[3] NDA 020788, Submission Cover Letter at 1-2.
[4] Propecia Medical Officer's Review, Part 1, Page 5 (December 19, 1997).
[5] Propecia Medical Officer's Review, Part 3, Page 62 (December 19, 1997).
[6] Propecia Medical Officer's Review, Part 3, Page 66 (December 19, 1997).
[7] Propecia Medical Officer's Review, Part 3, Page 72 (December 19, 1997).
[8] Propecia Medical Officer's Review, Part 3, Page 99 (December 19, 1997).
[9] Propecia Medical Officer's Review, Part 3, Page 98 (December 19, 1997).

1. Labeling Supplements to Propecia (NDA 020788) Regarding Depression

On July 16, 2010, Merck submitted a changes-being-effected (CBE) supplement (CBE-0)[10] to include the term "depression" in the ADVERSE REACTIONS section of product labeling.[11] Merck proposed this labeling change based on results of a search of the Worldwide Adverse Experience System database for studies conducted in patients treated with finasteride 0.2 mg and 1 mg tablets (Propecia) using terms related to depression and suicide.[12] On March 11, 2011, FDA approved the addition of the term "depression" to the ADVERSE REACTIONS (Postmarketing Experience) section of the labeling and Patient Package Insert.[13]

2. Labeling Supplements to Propecia (NDA 020788) Regarding Sexual Adverse Events

In 2011 and 2012, Merck submitted two supplements to the Propecia NDA, S-021 and S-023, regarding sexual adverse events. Supplement S-021 was a CBE supplement that added "erectile dysfunction that continued after discontinuation of treatment," to the ADVERSE REACTIONS (Postmarketing Experience) section of the package insert and to the patient labeling.[14] Supplement S-023 was a Prior Approval Supplement (PAS) to the NDA that proposed the addition of "male infertility and/or poor seminal quality (normalization or improvement of seminal quality has been reported after discontinuation of finasteride)," to the ADVERSE REACTIONS (Postmarketing Experience) section of the package insert and to the patient package insert.[15] Both S-021 and S-023 were approved on April 11, 2012.[16]

On September 18, 2018, Merck submitted a PAS (S-028) that proposed the addition of an adverse event, "hematospermia," to the ADVERSE REACTIONS (Postmarketing Experience) section of the prescribing information.[17] The Agency approved S-028 on June 15, 2021.

B. Proscar (NDA 020180)

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[10] Under §§ 314.70(c)(6) and 601.12(c)(5) (21 CFR 314.70(c)(6) and 601.12(c)(5)), an applicant may commence distribution of a drug product manufactured using a change proposed in a CBE-0 supplement after FDA receives that supplement.

[11] Approval Package for NDA 020788/S-017, Clinical Review of NDA 020788 Supplemental Label Request at 20, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/020788Orig1s017.pdf.

[12] Approval Package for NDA 20788/S-017, Clinical Review of NDA 020788 Supplemental Label Request at 20, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/020788Orig1s017.pdf,

[13] Supplement Approval Letter, NDA 020788/S-017 (March 11, 2011). https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020788s017ltr.pdf.

[14] Supplemental Approval Letter, NDA 020788/S-020, S-021, S-023 (April 11, 2012) https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/020788s020,s021,s023ltr.pdf.

[15] Supplemental Approval Letter, NDA 020788/S-020, S-021, S-023 (April 11, 2012), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/020788s020,s021,s023ltr.pdf.

[16] Supplemental Approval Letter, NDA 020788/S-020, S-021, S-023 (April 11, 2012), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/020788s020,s021,s023ltr.pdf.

[17] Supplement Approval Letter, NDA 020788/S-028 (June 15, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/020788Orig1s028ltr.pdf.

On June 19, 1992, finasteride was first approved under Merck's NDA for Proscar tablets, 5 mg (NDA 020180), for the treatment of symptomatic BPH.[18] On January 16, 2013, a PAS (0-43) was approved to provide for changes to the ADVERSE REACTIONS (Postmarketing Experience) section of Proscar labeling related to sexual dysfunction that continued after discontinuation of treatment.[19] The PAS changed the label from stating only that erectile dysfunction had been reported to continue after discontinuation of treatment with Proscar to "sexual dysfunction, including erectile dysfunction, decreased libido, and ejaculation disorders (e.g., reduced ejaculate volume)" had been reported to continue after discontinuation of treatment with Proscar. In addition, a separate paragraph was included in ADVERSE REACTIONS (Postmarketing Experience) stating that "orgasm disorders" had been reported to continue after treatment with finasteride at lower doses used to treat MPB.[20]

On September 18, 2018, Merck submitted a PAS (S-047) that proposed the addition of an adverse event, "hematospermia," to the ADVERSE REACTIONS (Postmarketing Experience) section of the prescribing information.[21] The Agency approved S-047 on June 15, 2021.

II. LEGAL AND REGULATORY BACKGROUND

A. Standard for Withdrawal of NDA or ANDA Approval

Section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(e)) establishes the circumstances under which the Agency shall, after due notice and opportunity for a hearing, withdraw approval of an NDA or abbreviated new drug application (ANDA). With respect to safety concerns, the Agency shall withdraw approval of an NDA or ANDA if it finds either of the following:

> that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; [or]
> that new evidence of clinical experience, not contained in such application or not available to the [Agency] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the [Agency] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved.[22]

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[18] The Petition requests that FDA take certain actions with respect to Proscar, previously owned by Merck. On December 4, 2020, FDA received a notice of transfer of ownership of the Proscar NDA (020180) from Merck Sharp & Dohme Corp, a Subsidiary of Merck & Co, Inc., to Organon LLC (Organon).
[19] Supplement Approval Letter, NDA 020180/S-043 (Jan. 15, 2013), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/020180Orig1s043ltr.pdf.
[20] Compare April 2012 Proscar Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020180s040s041s042lbl.pdf, to Jan. 2013 Proscar Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020180s043lbl.pdf.
[21] Supplement Approval Letter, NDA 020788/S-028 (June 15, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/020788Orig1s028ltr.pdf.
[22] Section 505(e)(1) and (2) of the FD&C Act; see also § 314.150(a)(2)(i) and (ii) (21 CFR 314.150(a)(2)(i) and (ii)).

With respect to effectiveness, the Agency shall withdraw approval of an NDA or ANDA if it finds "that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof."[23]

B. Prescription Drug Labeling

1. Overview of Relevant Statutory and Regulatory Requirements

Under the FD&C Act and FDA regulations, the Agency makes decisions on the approval of marketing applications, including supplemental applications, for drug products based on a comprehensive scientific evaluation of the drug product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling (see section 505(d) of the FD&C Act (21 U.S.C. 355(d))). An NDA is "required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source" (§ 314.50 (21 CFR 314.50)). An NDA also must contain the applicant's proposed text of the labeling, including "annotations to the information in the summary and technical sections of the NDA that support the inclusion of each statement in the labeling" (§ 314.50(c)(2)(i)).

FDA-approved drug product labeling summarizes the essential information needed for the safe and effective use of the drug (see § 201.56(a) (21 CFR 201.56(a))) and reflects FDA's finding on the safety and effectiveness of the drug under the labeled conditions of use. The primary purpose of FDA-approved labeling for prescription drugs is to provide health care practitioners with the essential scientific information needed to facilitate prescribing decisions, thereby enhancing the safe and effective use of prescription drug products and reducing the likelihood of medication errors. Prescription drug labeling is directed to health care practitioners but may also include additional FDA-approved labeling directed at the patient or caregiver (commonly referred to as patient labeling).

As part of its review of an NDA for a prescription drug, FDA reviews the proposed text of the labeling submitted by the applicant.[24] FDA communicates with the applicant about "scientific, medical, and procedural issues that arise" in the course of its review.[25] The "[d]evelopment of final labeling" generally is "an iterative process between the applicant and FDA" involving a series of communications regarding the proposed text of the draft labeling for the proposed product.[26] FDA may send an information request to the applicant requesting responses to questions or additional data or information based on the Agency's review of the draft labeling. FDA may recommend substantive revisions to data and information described in draft labeling

[23] Section 505(e)(3) of the FD&C Act; see also § 314.150(a)(2)(iii). Additional circumstances under which FDA shall or may withdraw approval of an NDA or ANDA are identified in section 505(e) of the FD&C Act; see also § 314.150(a)(2)(iv) and (v).
[24] See 21 CFR 314.50(e)(2)(ii) and (*l*)(1)(i).
[25] 21 CFR 314.102(a).
[26] See Center for Drug Evaluation and Research, CDER 21st Century Review Process: Desk Reference Guide, available at https://www.fda.gov/media/78941/download.

based on the Agency's evaluation and analysis of data submitted in the application (including an amendment or supplement to the application) or otherwise available to the Agency. This may include, for example, recommended revisions to the presentation of clinical study data to reflect FDA's statistical reanalysis of submitted data. This also may include, for instance, recommendations to add or remove safety-related information; recommendations to modify safety-related information to clarify the nature, severity, and frequency of the risk; or, as applicable, steps to prevent, mitigate, or manage the risk. FDA also may recommend nonsubstantive clarifying revisions to draft labeling—for example, to communicate a risk more clearly and effectively to health care practitioners.

2. BOXED WARNING

A BOXED WARNING may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury, because this information is especially important for a health care practitioner to consider in assessing the risks and benefits of a drug (see § 201.57(c)(1) (21 CFR 201.57(c)(1)). The BOXED WARNING must briefly explain the risk and then refer to the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section, where the risk is explained in more detail (see § 201.57(c)(1)). As FDA has explained in guidance,[27] a BOXED WARNING is ordinarily used to highlight one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug[; or]
- There is a serious adverse reaction[28] that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)[; or]
- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted.

3. CONTRAINDICATIONS

[27] See FDA guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (October 2011), available at https://www.fda.gov/media/71866/download (Warnings Guidance). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[28] FDA applies the definition of *serious* in § 314.80(a) (21 CFR 314.80(a)). A serious adverse drug experience is defined as "[a]ny adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition" (§ 314.80(a)).

The CONTRAINDICATIONS section must describe any situations in which the drug should not be used because the risk of use "clearly outweighs any possible therapeutic benefit."[29] This section should include observed and anticipated risks, but must not include theoretical risks.[30] This section could include, for example, a situation where animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrate that the drug has teratogenic effects) and those risks outweigh any potential benefit of the drug.[31]

4. WARNINGS AND PRECAUTIONS

The WARNINGS AND PRECAUTIONS section must describe "clinically significant adverse reactions," other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur when "reasonable evidence of a causal association" between the drug and such hazards exists.[32] FDA regulations require that the labeling "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." [33] FDA adopted that standard in part to "prevent overwarning" of potential risks, which, if included in the WARNINGS AND PRECAUTIONS section, could dilute other "more important warnings" or "deter appropriate use" of the drug.[34] FDA typically reserves this section for a "discrete set" of hazards serious enough to affect prescribing decisions.[35] FDA regulations provide that a "specific warning relating to a use not provided for under the INDICATIONS AND USAGE section may be required by FDA in accordance with sections 201(n) [21 U.S.C. 331(n)] and 502(a) [21 U.S.C. 352(a)] of the [FD&C Act] if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard."[36]

5. ADVERSE REACTIONS

The ADVERSE REACTIONS section describes "the overall adverse reaction profile of the drug."[37] FDA's regulations define an adverse reaction, for purposes of prescription drug labeling, as "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence."[38] The threshold for including an adverse reaction in this section is lower than that for the WARNINGS AND PRECAUTIONS section: An adverse reaction must be listed if "some basis" exists "to

[29] § 201.57(c)(5).
[30] See § 201.57(c)(5); see also Warnings Guidance at 8.
[31] See Warnings Guidance at 8-9.
[32] § 201.57(c)(6)(i).
[33] § 201.57(c)(6)(i).
[34] Preamble to final rule, "Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices" (73 FR 49603 at 49605–49606, August 22, 2008).
[35] See Warnings Guidance at 3.
[36] § 201.57(c)(6)(i).
[37] § 201.57(c)(7).
[38] Id.

believe there is a causal relationship between the drug and the occurrence of the adverse event."[39]

C. Postmarketing Safety Surveillance: Expectations for Application Holders and FDA Review

All drugs have risks, and health care practitioners and patients must balance the risks and benefits of a drug when making decisions about medical therapy. As a drug is used post-approval more widely and under diverse conditions, new information regarding the risks and benefits of a drug may become available. This information may include new risks or new information about known risks. Accordingly, all application holders are required to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.[40] Application holders must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers, and must comply with applicable reporting and recordkeeping requirements (see, e.g., § 314.80(b), (c), and (j)).[41] FDA guidance for industry explains that "[a]fter a [safety] signal is identified, it should be further assessed [by the application holder] to determine whether it represents a potential safety risk and whether other action should be taken."[42]

FDA employs a multidisciplinary staff of health care professionals, epidemiologists, and other scientists to review adverse drug experience data by a variety of methods. FDA applies principles of risk-based safety surveillance after the approval of a drug and monitors the benefit-risk profile throughout the product life cycle and takes regulatory action (e.g., requesting or requiring revisions to product labeling, communicating new safety information to the public, requiring or modifying REMS, withdrawing approval of the product) as appropriate.

Application holders are required to submit periodic adverse drug experience reports to FDA at regular intervals for review.[43] Periodic adverse drug experience reports may supplement the spontaneous reports available to FDA reviewers for identifying potential safety signals and learning about potential changes in the benefit-risk profile for marketed products.[44] Application

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[39] Id.

[40] See, for example, § 314.80(b).

[41] FDA also receives adverse drug experience reports directly from health care practitioners, researchers, consumers, and others (e.g., family members and lawyers). FDA learns about developments related to approved drugs through a variety of other sources. See, e.g., Appendix A to FDA guidance for industry *Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act* (July 2013), available at https://www.fda.gov/media/116594/download.

[42] See FDA guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005) at 9, available at https://www.fda.gov/media/71546/download.

[43] § 314.80(c)(2).

[44] There are inherent limitations to a voluntary reporting system for adverse events associated with the use of a drug, including, but not limited to, underreporting, duplicate reporting, and reporting biases. Furthermore, for any given

holders also must comply with requirements for other postmarketing reports under § 314.81 (21 CFR 314.81) and section 505(k) of the FD&C Act. These requirements include submission of an annual report that includes a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product and a description of actions the applicant has taken or intends to take as a result of this new information (e.g., if appropriate, proposed revisions to product labeling (see § 314.81(b)(2)(i)).[45]

1. Safety-Related Labeling Changes

Application holders have an ongoing obligation to ensure that their drug product labeling is accurate and up-to-date.[46] When new information becomes available that causes information in labeling to be inaccurate, false, or misleading, the application holder must take steps to change the content of its labeling.[47] For example, the labeling "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."[48] A drug is misbranded in violation of the FD&C Act when its labeling is false or misleading or does not provide adequate warnings.[49]

After FDA has approved an NDA, two mechanisms exist for an applicant to substantively revise its labeling, both of which require the application holder to file a supplemental application for FDA approval. For most substantive changes to product labeling, an application holder is required to submit a prior approval supplement and receive approval for the proposed labeling changes before distributing revised product labeling.[50]

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report, the reported adverse events may not be causally related to the products reported to have been taken. The event may have been related, for example, to the underlying disease being treated, to other medical conditions, or to another product taken at the same time. The number of cases reported to FDA's Adverse Event Reporting System cannot be used to calculate the incidence rates, to estimate drug risk for a particular product, or to compare risks between products.

[45] An annual report also is required to contain, among other things:

- "Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product" (§ 314.81(b)(2)(v))
- "Published clinical trials of the drug (or abstracts of them) . . . and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant" (§ 314.81(b)(2)(vi)(*a*))
- "Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant" (§ 314.81(b)(2)(vi)(*b*))

[46] See *Wyeth v. Levine*, 555 U.S. 555, 570–71 (2009) ("It is a central premise of the [FD&C Act] and the FDA's regulations that the manufacturer bears responsibility for the content of its label[ing] at all times"); see also section 505(o)(4)(I) of the FD&C Act and § 201.56(a)(2) of the regulations.

[47] See §§ 201.56(a)(2) and 314.70 (21 CFR 314.70).

[48] § 201.57(c)(6)(i).

[49] See sections 301(a) and (b) and 502(a), (f), and (j) of the FD&C Act (21 U.S.C. 331(a) and (b) and 352(a), (f), and (j).

[50] § 314.70(b).

FDA may also initiate safety-related labeling changes on its own. FDA may issue a supplement request letter in which the Agency requests that an application holder make certain labeling changes, typically in response to a safety review conducted by FDA to assess a potential association between a drug or drug class and certain adverse events. The Agency may recommend specific changes to the labeling for the application holder's consideration or request that the applicant further evaluate the safety concern and propose text to address the risk.

Section 505(o)(4) of the FD&C Act authorizes FDA to require certain holders of approved applications for prescription drug products to make safety labeling changes if the Agency becomes aware of "new safety information" that FDA believes should be included in the drug's labeling. New safety information (NSI) is information or other scientific data deemed appropriate by the Agency:

> about a serious risk or an unexpected serious risk associated with use of the drug that the [Agency] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since [a] risk evaluation and mitigation strategy (REMS) [for the drug] was required, or since the last assessment of the approved REMS for the drug[.]

Section 505-1(b)(3) of the FD&C Act (21 U.S.C. 355-1).

Application holders have an opportunity to object to such labeling changes (see section 505(o)(4)(B) of the FD&C Act) and may enter into discussions to reach agreement on whether the labeling for the drug should be modified to reflect the NSI. FDA has the authority to issue an order requiring that the safety labeling changes be made. The standard for new safety information that may trigger an FDA-initiated safety labeling change required under section 505(o)(4) of the FD&C Act is not the same as newly acquired information under the CBE-0 pathway.

2. Adding a Risk Evaluation and Mitigation Strategy

Section 505-1 of the FD&C Act authorizes FDA to require a REMS if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks. A REMS is a required risk management strategy that employs tools beyond prescribing information to ensure that the benefits of a drug outweigh its risks. A REMS may require a Medication Guide (or patient package insert) to provide risk information to patients[51] and/or a communication plan to disseminate risk information to health care providers.[52] FDA may also require certain Elements to Assure Safe Use (ETASU) when such elements are necessary to mitigate specific serious risks associated with a drug.[53] The ETASU may include, for example, requirements that health care providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other

[51] Section 505-1(e)(2) of the FD&C Act.
[52] Section 505-1(e)(3) of the FD&C Act.
[53] Section 505-1(f)(1) of the FD&C Act.

documentation of safe-use conditions. [54] FDA can require a REMS at the time of initial approval of an NDA or after the drug has been approved if FDA becomes aware of new safety information[55] about a drug and determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.[56]

III. DISCUSSION

A. Requested Labeling Changes to Propecia

Your Petition requests that FDA require the "immediate revision of the Propecia product labeling (and generic versions of Propecia, 1 mg, for androgenic alopecia) to warn of serious and severe risks, and to amend false and misleading information" (Petition at 1).

Your Petition identifies both psychoneurocognitive effects of Propecia and sexual effects of Propecia, and you claim that the labeling for these effects is "dangerously deficient" (Petition at 119). As such, you ask for labeling changes to the WARNINGS AND PRECAUTIONS, BOXED WARNING, CONTRAINDICATIONS, and CLINICAL STUDIES sections with respect to both psychoneurocognitive and sexual effects. Additionally, you request that corresponding changes be made to the CLINICAL PHARMACOLOGY section to accurately describe the mechanism of action and pharmacodynamics of finasteride. Below, we first respond to the requests for changes to the labeling based on the psychoneurocognitive literature and adverse events; then we discuss the requested labeling changes with respect to the sexual adverse events and literature; and, finally, we discuss the changes requested regarding the mechanism of action and pharmacodynamics of finasteride.

1. Proposed Labeling Changes With Respect to Psychoneurocognitive Effects of Propecia

You argue that FDA should require changes to the Propecia labeling as a result of the psychoneurocognitive adverse events associated with finasteride treatment. You assert that depression with suicidal ideation develops with finasteride use, persists indefinitely after discontinuation of finasteride treatment, and occasionally leads to completed suicide (Petition at 77). To this end, you assert that patients taking finasteride have altered neuroactive steroid levels in plasma and cerebrospinal fluid and the decreased allopregnanolone levels in cerebrospinal fluid correlate with major depression and a positive depression treatment response (Petition at 80). You also argue that patients taking finasteride have neurobiological abnormalities in the central nervous system that are consistent with major depressive disorder. Because of these changes to the neurological system caused by finasteride use, you recommend updates to the WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, and ADVERSE REACTIONS sections of labeling. Below, we discuss the references you submitted in support of your suggested labeling changes.

[54] Section 505-l(f)(3) of the FD&C Act.
[55] Section 505-1(b)(3) of the FD&C Act.
[56] Section 505-1(a) of the FD&C Act.

Finasteride is a selective inhibitor of type II 5α-reductase. In the brain, 5α-reductase converts progesterone to allopregnanolone, which is a neuroactive steroid and positive allosteric modulator of $GABA_A$ receptors. Evidence that exogenous allopregnanolone can have an antidepressant effect led to the approval of brexanolone (chemically identical to allopregnanolone) for postpartum depression. However, there have been no consistently observed correlations between endogenous levels of allopregnanolone and symptoms of postpartum depression. You cited a study by Uzunova (1998) to demonstrate how low allopregnanolone levels are observed in people with depression, but those levels increased after antidepressant treatment (Petition at 78).[57] However, the study was extremely small (15 people with depression and only 3 controls) and did not include any finasteride exposures. Your Petition also includes two citations (Duskova 2009 and 2010) describing neurosteroid changes (including a decrease in allopregnanolone) in patients with BPH exposed to finasteride, but these studies did not include psychiatric measures or control groups.[58] Finally, the findings from two (Caruso 2014, Basaria 2016) of the six neurosteroid studies you provided are not consistent regarding hypothesized changes in neurosteroid levels after finasteride exposure.[59]

Notably, one study you cited (Welk 2017) reported an increased hazard ratio for both depression and self-harm (defined as emergency department visits for a suicide attempt or parasuicide behavior or psychiatric hospital admission for recent self-harm or thoughts of self-harm) in a large retrospective study of elderly men starting a 5α-reductase inhibitor for BPH compared to a matched group.[60] This study did not find an association between completed suicides and 5α-reductase inhibitors and did not include younger men or those taking Propecia for androgenic alopecia. Another large retrospective study of men starting a 5α-reductase inhibitor in the Veterans Health Administration found no association between 5α-reductase inhibitors and depression.[61] Additionally, in phase 3 clinical studies of Propecia for androgenic alopecia (over 900 subjects each in randomized, double-blind Propecia and placebo treatment groups), one subject each, both receiving placebo, discontinued the study due to depression and emotional lability. No serious psychiatric adverse events were reported. In the placebo treatment group, one patient each (0.1%) experienced depression and emotional change. In the Propecia treatment group, one patient (0.1%) experienced depressive disorder.

Some of the strongest evidence you cited for a causal association between finasteride and depression is from two cases where depression started soon after starting finasteride, resolved

[57] Uzunova V et al., Increase in the CSF Content of Neurosteroids in Patients With Unipolar Major Depression Who Are Receiving Fluoxetine or Fluvoxamine, Proc Natl Acad Sci (1998), Vol. 95, pp. 3239-3244.
[58] Duskova M et al., Finasteride Treatment and Neuroactive Steroid Formation, Prague Med Rep (2009), Vol. 110(3), pp. 222-230; Duskova M et al., The Influence of Low Dose Finasteride, a Type II 5α-Reductase Inhibitor, on Circulating Neuroactive Steroids, Horm Mol Biol Clin Invest (2010), Vol. 1(2), pp. 95-102.
[59] Caruso D et al., Patients Treated for Male Pattern Hair With Finasteride Show, After iscontinuation of the Drug, Altered Levels of Neuroactive Steroids in CSF and Plasma, J Ster Biochem Mol Biol (2014), Vol. 146, pp. 74-79; Basaria S et al., Characteristics of Men Who Report Persistent Sexual Symptoms After Finasteride Use for Hair Loss (2016); pp. 4669-4680.
[60] Welk B et al., Association of Suicidality and Depression With 5α-Reductase Inhibitors, JAMA Intern Med (2017), Vol. 177(5), pp. 683-691.
[61] Dyson TE et al., Lack of Association Between 5α-Reductase Inhibitors and Depression. J Urol 2020; 204(4):793-798.

upon finasteride discontinuation, and recurred with drug re-challenge.[62] However, the study is a retrospective case series, and, although the authors report the observed sexual dysfunction in their sample was mild, it is unclear whether the cases of positive re-challenge were confounded by a recurrence of sexual dysfunction.

The literature you cited (e.g., case reports, retrospective observational studies, and pharmacovigilance studies) does not provide reasonable evidence to support a causal association between finasteride and depression. Most studies were small and lacked baseline measures, prospective assessments, a control group, the ability to account for confounding factors, and the presence of correlated health conditions such as sexual dysfunction. Sexual dysfunction and depression are closely linked and androgenic alopecia itself may be associated with negative psychological effects. Psychiatric symptom onset relative to 5α-reductase inhibitor initiation and treatment duration were variable (e.g., resolution of symptoms with discontinuation of Propecia, symptom onset after discontinuation of Propecia, continuation of symptoms years after discontinuation of Propecia). Although it is possible that this variability in depression onset may represent some long-lasting risk after 5α-reductase exposure, this variability is likely influenced by recall and attribution biases, especially due to the extensive publicity of finasteride safety issues.

a. CONTRAINDICATIONS

Your Petition requests that FDA require Organon[63] to add to the CONTRAINDICATIONS section of labeling that Propecia should not be used in any individual with depression, and relatedly, a BOXED WARNING that Propecia should be immediately discontinued in any individual who develops depression while taking Propecia (Petition at 2).

As noted in section III.A.1, the descriptions of depression in the literature that you provided are limited and no specific at-risk population can be identified. Although some cases of depression occurred in patients with a history of depression, not all cases did. Additionally, the literature does not provide the number of people with a history of depression who were prescribed finasteride and did not develop subsequent depression. This information is necessary to determine risk.

The literature you cited is, at best, inconclusive as to whether finasteride should be used by individuals with depression. For the Agency to include a contraindication in the labeling, the risk of use "clearly outweighs any possible therapeutic benefit."[64] Depression is already included in the finasteride labeling in the ADVERSE REACTIONS (Postmarketing Experience) section, and the information provided in the studies referenced in your Petition does not denote a defined population of patients for whom the use of finasteride would be contraindicated.

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[62] Altomare G and Capella GL, Depression Circumstantially Related to the Administration of Finasteride for Androgenetic Alopecia, J Dermatol (2002), Vol. 29, pp. 665-669.
[63] As noted in footnote 2, NDA 020788 is now owned by Organon and we are therefore interpreting all requests involving Merck to be requests involving Organon.
[64] § 201.57(c)(5).

Additionally, the descriptions of depression in the literature do not provide evidence of mitigating effects of medication discontinuation on depressive symptoms. Based on your citations, some cases describe resolution of symptoms with finasteride discontinuation and other cases describe ongoing depressive symptoms despite discontinuing finasteride. Discontinuation of potentially problematic medication is an appropriate first step for any adverse reaction, but discontinuation may or may not mitigate the risk of depression for patients taking finasteride. Therefore, we do not agree that a BOXED WARNING should be added to the labeling for Propecia to recommend discontinuing its use in any individual who develops depression while taking Propecia.

b. WARNINGS AND PRECAUTIONS

More specifically, your Petition requests that FDA require that Organon adds a new WARNINGS AND PRECAUTIONS and a concomitant BOXED WARNING to the labeling for Propecia to alert patients of risks of major depressive disorder and suicidal ideation/behavior (Petition at 1-2).

The addition of major depressive disorder in the WARNINGS AND PRECAUTIONS section and in a BOXED WARNING are not justified. The literature you cited in your Petition has significant methodological limitations, and there is not reasonable evidence to support a causal association between major depressive disorder and the use of Propecia. Therefore, we deny your request to add major depressive disorder to the WARNINGS AND PRECAUTIONS section of labeling. Additionally, since a BOXED WARNING briefly describes risks that are further detailed in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section, there is no underlying basis for a BOXED WARNING for a risk is not described in either of those sections. Clinicians and patients are adequately informed of the potential for major depressive disorder because it is listed within the ADVERSE REACTION (Postmarketing Experience) section of labeling.

FDA also denies your request to require Organon to add suicidal ideation/behavior to the WARNINGS AND PRECAUTIONS section or as a BOXED WARNING. Again, the literature you cited in your Petition has significant methodological limitations, and there is not reasonable evidence to support a causal association between suicidal ideation/behavior and the use of Propecia. Therefore, we deny your request to require Organon to add suicidal ideation/behavior to the WARNINGS AND PRECAUTIONS section of labeling. Additionally, since a BOXED WARNING briefly describes risks that are further detailed in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section, there is no underlying basis for a BOXED WARNING for a risk not described in either of those sections.

c. ADVERSE REACTIONS

Your Petition requests that FDA require Organon to add language in section 6, ADVERSE REACTIONS, of the Propecia labeling. Specifically, with respect to psychiatric adverse events, you request that Organon add a warning for anxiety, cognitive function, and fatigue to ADVERSE REACTIONS (Postmarketing Experience) (Petition at 3).

The methodological limitations of the publications cited in support of the addition of anxiety, cognitive function, and fatigue to the ADVERSE REACTIONS section of the labeling are described in detail in section III.A.1. Anxiety, fatigue, and cognitive dysfunction are all associated with depression.[65] None of the cited publications demonstrated an association between anxiety, fatigue, or cognitive dysfunction and finasteride that was present when the patient did not also have depression. Specifically, one citation (Rahimi 2006) found an increased risk of anxiety in finasteride-treated patients, though not statistically significant, and one citation (Basaria 2016) found increased subjective complaints of memory issues but did not find a difference in objective measures of cognition between subjects on finasteride and controls.[66] Therefore, we decline to require Organon to add anxiety, cognitive function, and fatigue to the ADVERSE REACTIONS (Postmarketing Experience) section of the Propecia labeling.

However, based on our analysis contained in part and prompted by your Petition, including postmarketing reports, we are requiring that Organon change Propecia's labeling to add suicidal ideation/behavior to the ADVERSE REACTIONS (Postmarketing Experience) section. Based on the mechanism of action of finasteride, there is a possible tie between Propecia and suicide-related adverse events. While we could not conclude that there was reasonable evidence of a causal association between Propecia and suicidality, the mechanism of action and the suicide-related adverse events identified in FDA Adverse Event Reporting System (FAERS) support including suicidal ideation/behavior in the ADVERSE REACTIONS (Postmarketing Experience) section.

2. Proposed Labeling Changes With Respect to Sexual Adverse Events

Your Petition argues that finasteride causes several adverse events related to sexual and reproductive function. In particular, you claim that finasteride usage causes persistent and permanent erectile dysfunction, infertility and decreased spermatogenesis, penis disorders, testicular pain, breast enlargement, and breast tenderness. You assert that the labeling for Propecia and other finasteride, 1 mg and 5 mg, products is inadequate and that several sections of the labeling need to be updated, including the CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS sections.

In support of your arguments, you submitted evidence including case reports, meta-analyses, observational studies, epidemiological studies, and randomized controlled trials. We have reviewed each of your attachments in detail, and we decline to make the changes requested in your Petition for the reasons described below.

a. WARNINGS AND PRECAUTIONS

[65] American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596.

[66] Rahimi-Ardabili B et al., Finasteride Induced Depression: A Prospective Study, BMC Clin Pharmacol (2006), Vol. 6(7), pp. 1-6; Basaria S et al., Characteristics of Men Who Report Persistent Sexual Symptoms After Finasteride Use for Hair Loss (2016), pp. 4669-4680.

i. Erectile Dysfunction

Your Petition requests that FDA add a new WARNINGS AND PRECAUTIONS and an accompanying BOXED WARNING to the labeling for Propecia to alert patients and providers of risks, including persistent and permanent erectile dysfunction and the need to discontinue treatment in any individual who develops sexual dysfunction while taking Propecia (Petition at 1-2).

You contend that finasteride usage causes persistent and permanent erectile dysfunction, which also does not resolve with discontinuation of finasteride treatment (Petition at 47). In this regard, you request labeling changes to reflect persistent erectile dysfunction. You argue that large-scale, observational epidemiological studies and the testimony of a Merck regulatory executive support your request for labeling changes[67] (Petition at 47). You cite as support evidence from medical literature, case reports from the FAERS database, and studies documenting objective findings in patients. (Petition at 47). Your evidence for the addition of persistent and permanent erectile dysfunction and sexual dysfunction to the labeling, in general, is found in observational studies,[68] case series,[69] and meta-analyses.[70]

The observational studies and case series both contained deficiencies in study conduct, procedures, and methods. The methodological deficiencies of the observational studies and case

[67] Guo M et al., Persistent Sexual Dysfunction With Finasteride 1 mg Taken for Hair Loss, Pharmacother (2016), Vol. 36(11), pp. 1180-1184; Kiguradze T, Persistent Erectile Dysfunction in Men Exposed to the 5α-Reductase Inhibitors Finasteride or Dutasteride, PeerJ (2017), 5:e3020, DOI 10.7717/peerj.3020, pp. 1-31; In re: Propecia (Finasteride Products Liab. Litig. MDL 2331) Plaintiffs' Motion to Amend PPO No. 10 and Extend Discovery Deadline to Allow for Requests for Admission (2016 Jul 20), pp. 1-7, Exhibits A-F.

[68] Guo M et al., Persistent Sexual Dysfunction With Finasteride 1 mg Taken for Hair Loss, Pharmacother (2016), Vol. 36(11), pp. 1180-1184; Kiguradze T, Persistent Erectile Dysfunction in Men Exposed to the 5α-Reductase Inhibitors Finasteride or Dutasteride, PeerJ (2017), Vol. 5, pp. 1-31; La Marra F et al., Preliminary Evidence of a Peculiar Hormonal Profile in Men With Adverse Effects After Use of Finasteride Against Androgenetic Alopecia, Amer J Pathol (2012), Vol. 181, Suppl., Abstract EMD3; Di Loreto C et al., Immunohistochemical Evaluation of Androgen Receptor and Nerve Structure Density in Human Prepuce From Patients With Persistent Sexual Side Effects After Finasteride Use for Androgenetic Alopecia, PLoS One (2014), Vol. 9(6), pp. e1-e7; Cauci S et al., Androgen Receptor (AR) Gene (CAG)n and (GGN)n Length Polymorphisms and Symptoms in Young Males With Long-Lasting Adverse Effects After Finasteride Use Against Androgenic Alopecia, Sex Med (2016), Vol. 5, pp. e1-e11; Melcangi RC et al., Neuroactive Steroid Levels and Psychiatric and Andrological Features in Post-Finasteride Patients (2017) pp. 229-235. Irwig MS and Kolukula S, Persistent Sexual Side Effects of Finasteride for Male Pattern Hair Loss, J Sex Med (2011), Vol. 8, pp. 1747-1753; Irwig MS, Persistent Sexual Side Effects of Finasteride: Could They Be Permanent?, J Sex Med (2012), Vol. 9, pp. 2927-2932; Ganzer C et al., Persistent Sexual, Emotional, and Cognitive Impairment Post-Finasteride: A Survey of Men Reporting Symptoms, Amer J Men Health (2015), Vol. 9(3), pp. 222-228; Chiriaco G et al., An Observational Retrospective Evaluation of 79 Young Men With Long-Term Adverse Effects After Use of Finasteride Against Androgenetic Alopecia, Andrology (2016), Vol. 4, pp. 245-250.

[69] Traish AM et al., Adverse Side Effects of 5α-Reductase Inhibitors Therapy: Persistent Diminished Libido and Erectile Dysfunction and Depression in a Subset of Patients, J Sex Med (2011), Vol. 8, pp. 872-884; Moore T et al., Finasteride (PROPECIA®) and Persistent Side Effects, Inst Safe Medication Pract, Quarter Watch (2013), Data from 2012 Quarter 2, pp. 7-10; Ali AK et al., Persistent Sexual Dysfunction and Suicidal Ideation in Young Men Treated with Low-Dose Finasteride: A Pharmacovigilance Study, Pharmacother (2015), Vol. 35(7), pp. 687-695.

[70] Mella J et al., Efficacy and Safety of Finasteride Therapy for Androgenetic Alopecia: A Systematic Review, Arch Derm (2010), Vol. 146(10), pp. 1141-1150.

series include the absence of baseline sexual function testing; recall bias related to estimation of prior sexual function; missing clinical information and data; selection bias; small sample size; use of non-validated sexual function questionnaires and other patient-reported outcome instruments; lack of standardized, proper methods for assessing serum androgen concentrations; variable and overly broad diagnostic coding for sexual dysfunction; confounding by factors associated with use of finasteride (e.g., prostate disease, age); confounding by intercurrent events; and use of study endpoints without known clinical relevance. Additional deficiencies related to the studies include differential testing and evaluation of cases versus controls, arbitrary time cut points, and arbitrary subgroups.

Additionally, the observational studies you cite in your Petition do not provide reasonable evidence of a causal association between finasteride and persistent sexual dysfunction. For example, the Kiguradze study (2017) did not evaluate factors associated with resolution of persistent erectile dysfunction or loss of libido following discontinuation of finasteride.[71] The weaknesses of this study include unmeasured or uncontrolled confounding factors, potential differential reporting of sexual dysfunction outcomes among patients with finasteride exposure (i.e., reporting bias), and poorly documented statistical methods (classification tree models). In the Guo study (2016), resolution of sexual adverse events was not evaluated.[72] This study's limitations also include inconsistent inclusion and exclusion criteria for finasteride and omeprazole (comparator) cohorts, potential misclassification of persistent sexual dysfunction using a single code, lack of outcome algorithm validation, and potential differential reporting of persistent sexual dysfunction (i.e., reporting bias). Studies led by Irwig (2012a, 2011) recruited men from clinical practices and online forums who may have been motivated to respond to study surveys due to severe or persistent sexual adverse events;[73] additionally, these studies and another analysis by Chiriaco et al. (2016) excluded men who experienced possible finasteride-associated adverse events that resolved within 3 to 6 months after discontinuation.[74] As such, the findings from these studies cannot be generalized more broadly to all former finasteride users.

We also reviewed several other observational studies you cited and considered them low quality because they only reported descriptive statistics and had limitations — such as small sample size, use of self-reported data, selection bias, non-generalizability of findings, and confounding factors — that did not allow for an assessment of a potential causal relationship between finasteride and persistent sexual dysfunction.[75]

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[71] Kiguradze T, Persistent Erectile Dysfunction in Men Exposed to the 5α-Reductase Inhibitors Finasteride or Dutasteride, PeerJ (2017), Vol. 5, pp. 1-31

[72] Guo M et al., Persistent Sexual Dysfunction With Finasteride 1 mg Taken for Hair Loss, Pharmacother (2016), Vol. 36(11), pp. 1180-1184.

[73] Irwig MS and Kolukula S. Persistent Sexual Side Effects of Finasteride for Male Pattern Hair Loss. J Sex Med (2011), Vol. 8, pp. 1747-1753; Irwig MS. Persistent Sexual Side Effects of Finasteride: Could They be Permanent?, J Sex Med. (2012a Nov), Vol. 9(11), pp. 2927-2932.

[74] Chiriacò G et al., An Observational Retrospective Evaluation of 79 Young Men With Long-term Adverse Effects After Use of Finasteride Against Androgenetic Alopecia. Andrology (2016), Vol. 4(2), pp. 245-250.

[75] Basaria et al. 2016; Melcangi et al. 2017; Walf et al. Research Brief: Self-Reports of a Constellation of Persistent Antiandrogenic, Estrogenic, Physical, and Psychological Effects of Finasteride Usage Among Men, Am J Mens Health (2018) Vol. 12, pp.900-906; Pallotti et al., Androgenetic Alopecia: Effects of Oral Finasteride on Hormone Profile, Reproduction and Sexual Function, Endocrine (2020), Vol. 68, pp. 688-94.

In 2011, FDA evaluated FAERS cases[76] for patients reporting persistent sexual dysfunction that continued for at least 3 months after stopping finasteride, 1 mg. Based on these cases, FDA agreed with the Merck's labeling supplement and updated the labeling to include "sexual dysfunction that continued after discontinuation of treatment, including erectile dysfunction, libido disorders, ejaculation disorders, and orgasm disorders" in the ADVERSE EVENTS (Postmarketing Experience) section of the Propecia labeling. We continue to believe this pharmacovigilance analysis supports the inclusion of this information where it is currently listed, in the ADVERSE EVENTS (Postmarketing Experience) section of the Propecia labeling.

Three of your cited references pertain to the Proscar Long-Term Efficacy and Safety Study (PLESS) (Merck's Protocol 048; MK-906 Protocol PLESS trial study report authored by Waldstreicher and Wang; and the Wessels et al. publication).[77] PLESS (MK-906) was a 4-year controlled clinical study where 3,040 patients between the ages of 45 and 78 with symptomatic BPH and an enlarged prostate were evaluated for long-term safety of Proscar (finasteride, 5 mg). We agree that the Wessels analysis of PLESS is deficient. FDA conducted a review of the clinical study report and determined that the conclusions drawn from the report regarding the resolution of sexual adverse events are based on exploratory follow-up assessment and incomplete safety information.[78] The missing data were not accounted for, and therefore, the authors' conclusion is based on the limited dataset of those who were reached for the 6-month follow-up and who provided a sexual adverse event outcome at that time. The Waldstreicher and Wang clinical study report contains the only analysis that provides information from a finasteride, 5 mg, controlled study on resolution of sexual adverse events while on-study versus off-study.[79] The limited information provided on this topic appears to show uncommon resolution of sexual adverse events whether the patient received finasteride, 5 mg (adverse event resolution in 9 percent of participants on-study and 13 percent of participants off-study), or placebo (adverse event resolution in 10 percent of participants on-study and 24 percent of participants off-study), or whether the patient completed the study (adverse event resolution in 13 percent of participants on-study and 24 percent of participants off-study) or dropped out of the study (adverse event resolution in 9 percent of participants on-study and 10 percent of participants off-study). These results do not support your claim regarding finasteride, 5 mg effect on sexual adverse event resolution because the analysis that compared rates of sexual adverse event resolution between finasteride, 5 mg, and placebo at the 6-month post-study follow-up timepoint was based on incomplete safety information. As with the Wessels analysis, the researchers did not account for the missing data. Therefore, it is difficult to draw conclusions

[76] Pharmacovigilance Review (Sexual Dysfunction with Propecia), pp. 1-19 (June 2, 2011).
[77] The MK-906 Protocol PLESS trial 1991 reference is the final protocol for PLESS, which is a double-blind, parallel-controlled, randomized, multicenter study of approximately 3,000 patients aged 50-75 years old with benign prostatic hyperplasia who would be treated with either placebo or finasteride, 5 mg, daily for 4 years; The Waldstreicher J and Wang 1997 study included a clinical study report synopsis and a portion of the Safety section of the full clinical study report (CSR) for PLESS; The Wessels et al. 2003 study provided an analysis of sexual adverse events reported in PLESS.
[78] Wessells H et al., Incidence and Severity of Sexual Adverse Experiences in Finasteride and Placebo-Treated Men with Benign Prostatic Hyperplasia, Urology (2003), Vol. 61, pp. 579-584.
[79] Waldstreicher J and Wang D, Finasteride (MK-906) Clinical Study Report Synopsis (July 31, 1997, revised August 19, 1997).

based on the results from the Wessels analysis or the Waldstreicher and Wang clinical study report. Overall, the high incidence of unresolved sexual adverse events in PLESS likely reflects the known prevalence of erectile dysfunction and decreased libido in the older BPH population that was studied in PLESS.[80] In addition, the Wessels analysis of PLESS data showed a decreased incidence of sexual adverse events after Year 1, with no differences between the finasteride, 5 mg, and placebo groups for reports of sexual adverse events during Years 2 through 4. This result is contrary to your argument in the Petition that sexual adverse events did not decrease with longer duration of finasteride treatment in PLESS.

You provided animal studies in support of your claim that the inhibition of 5α-reductase interferes with androgen actions and may lead to persistent and irreversible adverse effects on human sexual function. Rittmaster et al., Shen et al., Corradi et al., and Zhang et al. did not demonstrate adverse or directly translatable effects, nor did they evaluate persistence or reversibility of any effects.[81] Oztekin et al. is irrelevant because they evaluated dutasteride in rats and failed to evaluate reversibility or observe any irreversible effects.[82] Schirar et al. is irrelevant because the study did not evaluate anything directly relevant to the claim that finasteride adversely affects human sexual function.[83] We conclude that, given limitations in their design, these animal studies do not support the addition of a warning related to persistent and irreversible sexual adverse events.

You submitted additional evidence in support of the labeling changes you requested in your December 1, 2020, Supplement to the Petition. You provided a summary of Reuter's investigation that was published on September 11, 2019, and you concluded that Merck's claim that the sexual adverse experiences resolved in men who discontinued Propecia was only based on a few men and long-term follow-up was not conducted. The Reuter's investigative news article does not provide reasonable evidence, such as a well-conducted, placebo-controlled clinical trial, to support the proposed labeling modification. Current Propecia labeling reflects

[80] Selvin E, Burnett AL and Platz EA, Prevalence and Risk Factors for Erectile Dysfunction in the United States. Am J of Medicine, Vol. 120(2) pp.151-159; Mulhall JP et al., Relationship Between Age and Erectile Dysfunction Diagnosis or Treatment Using Real-World Observational Data in the United States. Intl J of Clin Practice (2016), Vol. 70(12) p. 1012-1018.

[81] Rittmaster R et al., Effect of Finasteride, A 5α-Reductase Inhibitor, on Serum Gonadotropins in Normal Men, J Clin Endocrinol Metab (1992), Vol. 75, pp. 484-488; Shen Z et al., Effect of Androgen Deprivation on Penile Ultrastructure, Asian J Andrology (2003), Vol. 5, pp. 33-36; Corradi L et al., Increased Androgen Receptor and Remodeling in the Prostate Stroma After the Inhibition of 5-Alpha Reductase and Aromatase in Gerbil Ventral Prostate, Microsc Res and Technique (2009), Vol. 72, pp. 939-950; Corradi L et al., Long-Term Inhibition of 5-Alpha Reductase and Aromatase Changes the Cellular and Extracellular Compartments in Gerbil Ventral Prostate at Different Postnatal Ages, Intl J Exp Path (2009), Vol. 90, pp. 79-94; Zhang M et al., Effects of Oral Finasteride on Erectile Function in a Rat Model, J Sex Med (2012), Vol. 9(5), pp. 1328-1336 ; Zhang M et al., Long-term Oral Administration of 5α-Reductase Inhibitor Attenuates Erectile Function by Inhibiting Autophagy and Promoting Apoptosis of Smooth Muscle Cells in Corpus Cavernosum of Aged Rats, Urology (2013), Vol. 82(3), pp. 743.e9-743.e15.

[82] Oztekin C et al., Incomplete Recovery of Erectile Function in Rat After Discontinuation of Dual 5-Alpha Reductase Inhibitor Therapy, J Sex Med (2012), Vol. 9(7), pp. 1773-1781.

[83] Schirar A et al., Androgens Modulate Nitric Oxide Synthase Messenger Ribonucleic Acid Expression in Neurons of the Major Pelvic Ganglion in the Rat (1997) pp. 3093-3102.

the postmarketing reports of sexual dysfunction that continued after discontinuation of treatment, including erectile dysfunction, libido disorders, ejaculation disorders, and orgasm disorders.

The WARNINGS AND PRECAUTIONS section must describe "clinically significant adverse reactions," other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur when "reasonable evidence of a causal association" between the drug and such hazards exists.[84] FDA regulations require that the labeling "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."[85] The studies you cited in support of sexual adverse events and permanent and persistent erectile dysfunction fail to provide reasonable evidence to support a causal association between Propecia and persistent sexual dysfunction.

The various observational studies you cited contained many deficiencies in study design, methodology, and data analysis. The reported results from the randomized clinical trials also did not support your claims and had a significant amount of missing safety data that precluded drawing reliable conclusions on persistent erectile dysfunction. The animal data, in general, were not translatable nor relevant to the issue of human sexual dysfunction.

Your Petition requests that FDA require Organon to add an accompanying BOXED WARNING to the WARNINGS AND PRECAUTIONS section of the labeling for Propecia to alert patients and providers of permanent and persistent erectile dysfunction and the need to discontinue treatment in any individual who develops sexual dysfunction while taking Propecia. The studies you cited in support of sexual adverse events and permanent and persistent erectile dysfunction fail to provide reasonable evidence to support a causal association between Propecia and persistent sexual dysfunction. The various observational studies you cited contained many deficiencies in study design, methodology, and data analysis. The reported results from the randomized clinical trials, which are generally considered the strongest level of evidence, also did not support your claims on persistent erectile dysfunction. The animal data, in general, were not translatable or relevant to the issue of human sexual dysfunction. Therefore, we deny your request to require Organon to add persistent and permanent erectile dysfunction to the WARNINGS AND PRECAUTIONS section of labeling. Additionally, since a BOXED WARNING briefly describes risks that are further detailed in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section, there is no underlying basis for a BOXED WARNING for a risk not described in either of those sections.

ii. Spermatogenesis/Infertility

You request that FDA require Organon to add a WARNINGS AND PRECAUTIONS on the potential adverse effects of Propecia on spermatogenesis (Petition at 2). You contend that finasteride usage causes impaired spermatogenesis that continues after the discontinuation of the use of finasteride. You argue that the language in the labeling is misleading because it does not

[84] § 201.57(c)(6)(i)
[85] Id.

adequately document the role of DHT in spermatogenesis, the adverse effects of finasteride on fertility, and the reports of abnormal sperm parameters after discontinuation of finasteride (Petition at 93).

You provided references that were intended to address the role of DHT and 5α-reductase in spermatogenesis. These references were nonclinical studies in rats and human tissue studies.[86] Overall, the studies addressing the role of DHT and 5α-reductase in spermatogenesis were exploratory and mechanistic in nature and of unclear relevance to the treatment of adult men with finasteride. Specifically, Trybek et al. (2005) and Kolasa et al. (2011) demonstrated that finasteride (at high doses) can cause qualitative tissue changes to male rat reproductive tissues, but their findings are uninformative because of the lack of reversibility assessment, lack of functional correlate (i.e., there are no data showing that the changes have any effect in rats), and the qualitative reporting of results (i.e., the severity and frequency of any effects is unknown).[87] Dorrington and Fritz (1975) and O'Donnell et al. (1999) are irrelevant to this issue because neither examined finasteride, reversibility, or functional effects.[88] As such, none of these studies support adding information to the Propecia labeling related to finasteride-related infertility.

You also provide a case series, two case reports, and two studies of testicular histopathology that describe spermatogenesis and fertility in humans with genetic 5α-reductase deficiency.[89] Males with 5α-reductase deficiency are a poor model for otherwise healthy adult men taking finasteride for androgenic alopecia. This model is of limited relevance because the role of DHT in fertility

[86] Payne A et al., Formation of Dihydrotestosterone and Other 5α-Reduced Metabolites by Isolated Seminiferous Tubules and Suspension of Interstitial Cells in a Human Testis, J Clin Endocrinol Metab (1973), Vol. 37, pp. 448-453; Dorrington J and Fritz I, Cellular localization of 5alphareductase and 3alphahydroxysteroid Dehydrogenase in the Seminiferous Tubule of the Rat Testis, Endocrinology (1975), Vol. 96(4), pp. 897-899;Mahony M et al., Regional Distribution of 5α-reductase Type 1 and 2 mRNA Along the Human Epididymis, Fertil Steril (1998), Vol. 69(6), pp. 1116-1121; O'Donnell L, Testosterone-Dependent Restoration of Spermatogenesis in Adult Rats is Impaired by a 5α-Reductase Inhibitor, J Androl (1999), Vol. 20(1), pp. 109-117; Trybek G et al., Immunolocalization of Androgen Receptor in the Epididymis of Rats with Dihydrotestosterone Deficiency, Reproductive Biology (2005), Vol. 5(3), pp. 291-301;
Kolasa A et al., DHT Deficiency Perturbs the Integrity of the Rat Seminiferous Epithelium by Disrupting Right and Adherens Junctions, Folia Histochem Cytobiol (2011), Vol. 49(1), pp. 62-71.

[87] Trybek G et al., Immunolocalization of Androgen Receptor in the Epididymis of Rats With Dihydrotestosterone Deficiency, Reprod Biol (2005), Vol. 5(3), pp. 291-301; Kolasa A et al., DHT Deficiency Perturbs the integrity of the Rat Seminiferous Epithelium by Disrupting Right and Adherens Junctions, Folia Histochem Cytobiol (2011), Vol. 49(1), pp. 62-71.

[88] Dorrington J and Fritz I, Cellular Localization of 5lphareductase and 3Alphahydroxysteroid Dehydrogenase in the Seminiferous Tubule of the Rat Testis, Endocrinology (1975), Vol. 96(4), pp. 897-899; O'Donnell L, Testosterone-Dependent Restoration of Spermatogenesis in Adult Rats Is Impaired by a 5α-Reductase Inhibitor, J Androl (1999), Vol. 20(1), pp. 109-117.

[89] Cai L et al., Dihydrotestosterone Regulation of Semen in Male Pseudohermaphrodites with 5α-Reductase-2 Deficiency, J Clin Endocrinol Metab (1994), Vol. 79, pp. 409-414; Katz M et al., Paternity by Intrauterine Insemination with Sperm from a Man with 5α-Reductase-2 Deficiency, New Engl J Med (1997), Vol. 336(14), pp. 994-997; Nordenskjold A and Ivarsson S, Molecular Characterization of 5α-Reductase Type 2 Deficiency and Fertility in a Swedish Family, J Clin Endocrinol Metab (1998), Vol. 83, pp. 3236-3238; Steger K et al., Reversion of the Differentiated Phenotype and Maturation Block in Sertoli Cells in Pathological Human Testis, Human Reproduction (1999), Vol. 14(1), pp. 136-143; Hadziselimovic F and Dessouky N, Differences in Testicular Development Between 5α-Reductase 2 Deficiency and Isolated Bilateral Cryptorchidism, J Urol (2008), Vol. 180, pp. 1116-1120..

and spermatogenesis in these subjects, who have had lifelong deficiency of 5α-reductase and related prenatal developmental abnormalities, may be different from the role of DHT in fertility and spermatogenesis in normal adult men, who had normal prenatal development and normal levels of 5α-reductase for the duration of their lives.

Of the remaining references provided to describe finasteride's effect on fertility and spermatogenesis in men treated with finasteride: four were case reports;[90] one was an original FDA review of the Propecia NDA in which results from two studies of finasteride, 5 mg, in subjects with BPH were presented;[91] two were retrospective observational studies;[92] two were randomized, blinded, controlled study of finasteride, 5 mg, on sperm quality and sex hormone levels in healthy men;[93] and one was a study report.[94] These studies did not provide reasonable evidence to support a causal association for fertility or spermatogenesis.

You cited Merck semen production studies 012 and 056 as phase 3 trial data to support adding the adverse effect of spermatogenesis and the need to discontinue treatment in individuals who develop infertility. Merck studies 012 and 056 were submitted with the original Propecia application. The studies evaluated finasteride's effect on fertility in men who were treated with finasteride, 5 mg. The data in Merck 056 show that finasteride, 5 mg, causes a decrease in ejaculate volume. However, this effect resolves at some time between 36 and 60 weeks after discontinuation. There is no statistically significant difference between groups at 60 weeks after discontinuation. Our review of the data also shows no difference between treatment groups for mean percentage change in ejaculate volume at week 84 after drug discontinuation. Additionally, reduced ejaculate volume is a known effect of finasteride that is noted in the ADVERSE REACTIONS (Clinical Trials Experience) section of the labeling. Data from Merck study 012 showed that the decrease in total sperm per ejaculate is not statistically significantly different in the finasteride group compared to the placebo group after 12 weeks of use or after 12 weeks after drug discontinuation. Also, the decrease in percentage motile sperm was also not statistically significantly different in the finasteride group compared to the placebo group after 12 weeks of use or after 12 weeks of discontinuation.

Overall, the animal studies provided lack clinical significance and the clinical studies have methodological flaws that prevent an interpretation that concludes that there is an associative

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[90] Glina S et al., Finasteride-Associated Male Infertility, Revista do Hospital das Clínicas (2004), Vol. 59(4), pp. 203-205; Collodel G et al., Spermatozoa and Chronic Treatment With Finasteride: A TEM and FISH Study, Arch Androl: J Reproduct Syst (2007), Vol. 53, pp. 229-233; Liu KE et al., Propecia-Induced Spermatogenic Failure: A Report of Two Cases, Fertil Steril (2008); Vol. 90(3), pp. 849.e17-e19; Tu H and Zini A, Finasteride-Induced Secondary Infertility Associated With Sperm DNA Damage, Fertil Steril (2011), Vol. 95(6), pp. 2125.e13-14.

[91] Ko HS, FDA CDER Medical Review of Propecia NDA 20-788 (1997), pg. 7.

[92] Samplaski et al., Finasteride Use in the Male Infertility Population: Effects on Semen and Hormone Parameters (2013) pp. 1542-1546; Irwig MS, Androgen Levels and Semen Parameters Among Former Users of Finasteride With Persistent Sexual Adverse Events, JAMA Dermatol (2014), Vol. 150(12), pp.1361-1363.

[93] Overstreet J et al., Chronic Treatment With Finasteride Daily Does Not Affect spermatogenesis or semen production in young men, J Urology (1999), Vol. 162, pp. 1295-1300; Amory, J et al., The Effect of 5α-Reductase Inhibition With Dutasteride and Finasteride on Semen Parameters and Serum Hormones in Healthy Men, J Clin Endocrinol Metab (2007), Vol. 92, pp. 1659-1665.

[94] Waldstreicher J and Wang D, Finasteride (MK-906) Clinical Study Report Synopsis (July 31, 1997, revised August 19, 1997).

impact on spermatogenesis and fertility with the use of finasteride, 1 mg, in men for the treatment of androgenic alopecia. The results of studies that enroll men with 5α-reductase deficiency are of limited relevance because a study with results in males with 5α-reductase deficiency is not an appropriate model to infer results for otherwise healthy males taking finasteride for androgenic alopecia. The phase 3 clinical studies 056 and 012 were conducted with finasteride, 5 mg, and the results showed a small, reversible change in ejaculate volume that is likely not clinically significant.

The WARNINGS AND PRECAUTIONS section "is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management."[95] Adverse events must be included in the WARNINGS AND PRECAUTIONS section if there is reasonable evidence of a causal association between the drug and the adverse event; a causal relationship does not need to have been definitively established.[96] There is no reasonable evidence of a causal association between Propecia use and spermatogenesis or new safety signals pertaining to impaired spermatogenesis. Therefore, adding information about spermatogenesis to the WARNINGS AND PRECAUTIONS section is not warranted. The current labeling contains accurate and sufficient information to inform patients and prescribers about the related risk of decreased ejaculate volume from use of Propecia. Specifically, ADVERSE REACTIONS (Postmarketing Experience) include "male infertility and/or poor seminal quality."

b. CONTRAINDICATIONS

Your Petition requests that FDA require Organon to add labeling that states that Propecia is contraindicated for individuals with sexual dysfunction and male infertility (Petition at 2). Accordingly, you request a BOXED WARNING on the need to discontinue treatment in individuals who develop sexual dysfunction while taking Propecia and individuals who develop male infertility while taking Propecia (Petition at 2).

According to the regulations, the CONTRAINDICATIONS section of labeling "describe[s] any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit."[97] Risk of use outweighs benefit when "use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable."[98] Known hazards and not theoretical possibilities are required to be listed in the CONTRAINDICATIONS section.[99]

[95] Warnings Guidance at 3.
[96] 21 CFR 201.57(c)(6).
[97] 21 CFR 201.57(c)(5).
[98] Id.
[99] Id.

You request that FDA require Organon to update the CONTRAINDICATIONS section for Propecia to state that Propecia should not be used in any individual with sexual dysfunction. A product's CONTRAINDICATIONS must describe situations when a drug should not be used because the risk of use clearly outweighs any therapeutic benefit.[100] Men with preexisting sexual dysfunction were not excluded from Propecia clinical trials. Based on the low likelihood and mild to moderate severity of sexual dysfunction adverse events reported in Propecia clinical trials — as well as the lack of an established causal relationship between persistent or permanent erectile dysfunction and finasteride - the risk of finasteride-related sexual dysfunction does not outweigh any potential benefit to patients. In addition, the PLESS report stated that, among men taking finasteride, 5 mg, there was no difference in the incidence rates of sexual dysfunction between men with baseline sexual dysfunction and without baseline sexual dysfunction. Therefore, the risk related to sexual dysfunction does not outweigh any potential benefit to any patient taking Propecia. The current labeling identifies sexual dysfunctions, including decreased libido, erectile dysfunction, and ejaculation disorder, as adverse events associated with finasteride use as demonstrated in clinical trials, which are appropriately included in the ADVERSE REACTIONS (Clinical Trials Experience) section of the Propecia labeling. Additionally, the ADVERSE REACTIONS (Postmarketing Experience) section appropriately includes sexual dysfunctions, including erectile dysfunction, libido disorders, ejaculation disorders, and orgasm disorders.

You request that FDA require Organon to include a provision in the CONTRAINDICATIONS section for Propecia to not be used in any individual with male infertility. As described above, a product's CONTRAINDICATIONS must describe situations when a drug should not be used because the risk of use clearly outweighs any therapeutic benefit.[101] Even though diminished semen quality and male infertility was reported as an adverse event in postmarketing experience and reduced ejaculate volume is a known, reversible adverse reaction, there is no evidence to support a statement that the risk of male infertility is associated with the use of finasteride. Therefore, male infertility was appropriately noted in the Propecia labeling in the ADVERSE REACTIONS (Clinical Trials Experience and Postmarketing Experience) section. The risk of finasteride use includes ejaculation disorder (decreased volume of ejaculate), which is clearly outlined in the ADVERSE REACTIONS (Clinical Trials Experience) section of labeling, and male infertility and/or poor seminal quality, which is included in ADVERSE REACTIONS (Postmarketing Experience).

Therefore, the evidence submitted in your Petition does not support the addition of sexual dysfunction and male infertility to the CONTRAINDICATIONS section of the Propecia labeling. The totality of the evidence, including clinical trials, observational epidemiologic studies, FAERS reports, and animal data, failed to identify any new serious-associated safety risk to outweigh finasteride's therapeutic benefits. The studies referenced in the Petition failed to identify any new serious-associated safety risk to outweigh finasteride's therapeutic benefits.

Your Petition requests an accompanying BOXED WARNING to the CONTRAINDICATIONS

[100] Id.
[101] Id.

on the need to discontinue treatment in individuals who develop male infertility while taking Propecia and individuals who develop sexual dysfunction while taking Propecia. Since a BOXED WARNING briefly describes risks that are further detailed in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section, there is no underlying basis for a BOXED WARNING for a risk not described in either of those sections.

c. ADVERSE REACTIONS

Your Petition requests that FDA require Organon to delete or amend certain language in the ADVERSE REACTIONS section of the Propecia labeling. Specifically, you request the following changes (Petition at 2 and 3):

(1) Change the ADVERSE REACTIONS (Clinical Trials Experience) section to reflect the conclusion that resolution of sexual adverse reactions does not occur in all men, whether or not they discontinue therapy with Propecia. The current labeling states: "Resolution [of sexual adverse reactions] occurs in men who discontinued therapy with PROPECIA due to these side effects and in most who continued therapy." Your Petition proposes the following language: "Resolution [of sexual adverse reactions] does not occur in all men who discontinue therapy with PROPECIA due to these side effects and who continue therapy."

(2) Add information to the ADVERSE REACTIONS (Clinical Trials Experience) section that describes the sexual adverse event data from the phase 4 clinical trial with Propecia in men 41 to 60 years old and other clinical trials with finasteride, 1 mg and 5 mg, for benign prostatic hyperplasia.

(3) Add information to the ADVERSE REACTIONS (Clinical Trials Experience) section that describes the significant increase in penis disorders, testicular pain, breast enlargement and breast tenderness in men taking finasteride in the Prostate Long-term Efficacy and Safety Study.

(4) Remove from the ADVERSE REACTIONS (Postmarketing Experience) section the disclaimer about the voluntary reporting of adverse reactions being insufficient to establish a causal relationship between the reaction and the drug product.

(5) Change the labeling in the ADVERSE REACTIONS (Postmarketing Experience) section to reflect the conclusion that male infertility, spermatogenic failure and/or poor seminal quality do not resolve after discontinuation of therapy with Propecia.

i. ADVERSE REACTIONS (Clinical Trial Experience)

You request that FDA require Organon to make changes to the ADVERSE REACTIONS (Clinical Trials Experience) section to state that the resolution of sexual adverse reactions does not occur in all men, whether or not they discontinue therapy with Propecia. The current labeling states: "Resolution [of sexual adverse reactions] occurs in men who discontinued

therapy with PROPECIA due to these side effects and in most who continued therapy." Your Petition proposes the following language: "Resolution [of sexual adverse reactions] does not occur in all men who discontinue therapy with PROPECIA due to these side effects and who continue therapy" (Petition at 2).

As noted in section III.A.2.a. of this response, you submitted several references related to the continuation of sexual adverse events with Propecia discontinuation.[102] Of these studies, only a single reference citing data from the randomized, controlled PLESS study (Waldstreicher J and Wang D, 1997) addresses the issue of continuation of adverse sexual events. This reference included a clinical study report synopsis and a portion of the safety section of the full clinical study report for PLESS. As noted above, this reference does not support the claim regarding sexual adverse event resolution because the analysis conducted comparing rates of sexual adverse event resolution between finasteride and placebo at the 6-month, post-study, follow-up timepoint was based on incomplete safety information. The high incidence of unresolved sexual adverse events in PLESS likely reflects the known prevalence of erectile dysfunction and decreased libido in the older BPH population that was studied in PLESS.[103] PLESS's relevance to the effects of finasteride, 1 mg, in otherwise healthy men with androgenic alopecia is unclear. The Belknap (2015) and Mella (2010) studies were meta-analyses that did not address the persistence of sexual adverse events or the risk that sexual adverse events did not resolve in clinical trials of finasteride. The editorial reference by Moore (2015) did not address a possible causal relationship of finasteride with sexual dysfunction adverse events, their persistence, or lack of resolution after drug discontinuation.

Overall, you did not submit evidence that would require support updating the ADVERSE REACTIONS (Clinical Trials Experience) section regarding whether the sexual adverse reactions continue in men who discontinue therapy. The current labeling based on the review of the original data remains accurate and adequate.

You request that FDA require Organon to add information to ADVERSE REACTIONS (Clinical Trials Experience) that describes the sexual adverse event data from the phase 4 clinical trial with Propecia in men 41 to 60 years old and other clinical trials with finasteride, 1 mg and 5 mg, for BPH. You submitted study reports of published clinical trials related to the sexual adverse event data for finasteride used for the indications of BPH and androgenic alopecia.[104] Three of

[102] Waldstreicher J and Wang D, 1997; Belknap S et al., 2015; Mella JM et al., 2010; Moore TJ, 2015.
[103] Selvin E, Burnett AL and Platz EA, Prevalence and Risk Factors for Erectile Dysfunction in the United States. Am J of Medicine, Vol. 120(2) pp.151-159; Mulhall JP et al., Relationship Between Age and Erectile Dysfunction Diagnosis or Treatment Using Real-World Observational Data in the United States. Intl J of Clin Practice (2016), Vol. 70(12) p. 1012-1018.
[104] Gormley GJ et al., Effects of Finasteride (MK-906), a 5α-Reductase Inhibitor, on Circulating Androgens in Male Volunteers, J Clin Endocrinol Metab (1990), Vol. 70, pp. 1136-1141; Grino P et al., Finasteride for the Treatment and Control of Benign Prostatic Hyperplasia: Summary of Phase III Controlled Studies, Eur Urol (1994), Vol. 25 (supplement), pp. 24-28; Nickel J et al., Efficacy and Safety of Finasteride Therapy for Benign Prostatic Hyperplasia: Results of a 2-Year Randomized Controlled Trial (the PROSPECT Study), Canadian Med Assn J (1996), Vol. 155(9), pp. 1251-1259; Whiting D et al., Efficacy and Tolerability of Finasteride 1 mg in Men Aged 41 to 60 Years With Male Pattern Hair Loss, Eur J Derm (2003), Vol. 13, pp. 150-160.

these trials evaluated the effects of finasteride in men with BPH, and one evaluated finasteride in men with androgenic alopecia.

Gormley et al. (1990) compared 895 men aged 40 to 83 years with BPH who were treated with finasteride, 5 mg; finasteride, 1 mg; or placebo daily for 12 months.[105] Of the sexual adverse events listed (decreased libido, ejaculatory disorder, impotence, and orgasm dysfunction), only for decreased libido (6.0%, 4.7%, and 1.3% for 1 mg, 5 mg, and placebo, respectively) and ejaculatory disorder (4.4%, 4.4%, and 1.7% for 1 mg, 5 mg, and placebo, respectively) were the incidences for finasteride, 1 mg and 5 mg, significantly different from placebo. The sexual adverse events reported in this publication — impotence, diminished libido, and ejaculatory disorders — are known for Proscar and raise no new concerns. Whether the sexual adverse events reported in this study would occur in higher or lower percentages of otherwise healthy men with androgenic alopecia aged 41 to 60 years is not known. This study does not provide clinically meaningful data for Propecia prescribers, and we decline to add the data to the ADVERSE REACTIONS (Clinical Trials Experience) section of the Propecia labeling.

Grino et al. (1994) included 1,645 men with BPH treated with placebo, or finasteride, 1 mg or 5 mg, daily for 12 months.[106] Regarding safety, the authors reported a higher incidence of sexual dysfunction adverse events in subjects treated with finasteride (12.6% and 10.8% for subjects taking finasteride, 1 mg and 5 mg, respectively) than those treated with placebo (5.2%). The article states that sexual dysfunction was variably reported and was referred to as impotence, decreased libido, or ejaculation problems. The authors were unable to identify hormonal or age-related factors that could predict a higher chance of developing sexual dysfunction. They also note that the preliminary data suggest that sexual dysfunction associated with the use of finasteride is reversible on discontinuation of therapy. We cannot draw conclusions about the incidence of individual sexual adverse events in men 41 to 60 years old because the article describes the mean age, which was reported to be 64 to 66 years old. The study is also unclear as to the incidence of specific sexual dysfunction adverse events in men 41 to 60 years old being treated for androgenic alopecia with finasteride, 1 mg.

Nickel et al. (1996) studied 613 men aged 45 to 80 with BPH treated with finasteride, 5 mg, or placebo for 2 years.[107] The study showed the incidence of sexual dysfunction adverse events, such as ejaculation disorder (7.7% versus 1.6%) and impotence (15.8% versus 6.3%), were significantly higher in the finasteride, 5 mg, group than in the placebo group, respectively. The study's relevance to the effects of finasteride, 1 mg, in otherwise healthy men with androgenic alopecia is unclear given it studied effects of finasteride, 5 mg, in men with BPH. It is also not clear how finasteride affects the subgroup of men 60 years old or younger, because adverse events do not appear to be reported by age group. In addition, the study did not specify the type of ejaculation disorder, and one type of ejaculation disorder — decrease in ejaculate volume —

[105] Gormley GJ et al., Effects of Finasteride (MK-906), a 5α-Reductase Inhibitor, on Circulating Androgens in Male Volunteers, J Clin Endocrinol Metab (1990), Vol. 70, pp. 1136-1141.
[106] Grino P et al., Finasteride for the Treatment and Control of Benign Prostatic Hyperplasia: Summary of Phase III Controlled Studies, Eur Urol (1994), Vol. 25 (supplement), pp. 24-28.
[107] Nickel J et al., Efficacy and Safety of Finasteride Therapy for Benign Prostatic Hyperplasia: Results of a 2-Year Randomized Controlled Trial (the PROSPECT Study), Canadian Med Assn J (1996), Vol. 155(9), pp. 1251-1259.

is already included in the current labeling. This study does not provide clinically relevant data for Propecia prescribers, and there is no reason to add it to ADVERSE REACTIONS (Clinical Trials Experience) of the Propecia labeling.

Whiting et al. (2003) studied 424 men aged 41to 60 years with vertex male pattern hair loss who were treated with finasteride, 1 mg, or placebo daily for 24 months.[108] The study found that the most frequently reported sexual adverse event was decreased libido, although with a very small difference between groups (4.9% versus 4.4% in the finasteride and placebo groups, respectively). Ejaculation disorder (2.8% versus 0.7%) and erectile dysfunction (3.8% versus 0.7%) were both more frequent in the finasteride groups than in the placebo groups, respectively. You argue that the incidence of sexual adverse events in older men with androgenic alopecia (aged 41 to 60 years) reported in this study is greater than the incidence of sexual adverse events reported in younger men with androgenic alopecia (aged 18 to 41 years) in prior studies. We cannot draw meaningful conclusions based on comparisons of incidence of adverse events across these different studies because of differences in the study populations, study conduct, or some other unidentified factor that differed between the studies. For example, the incidences of erectile dysfunction (3.8%) and ejaculation disorders (2.8%) in the finasteride group in this study were greater compared to the incidences of the same adverse events in the labeled androgenic alopecia studies (1.3% and 1.2%, respectively), which may reflect the background incidence of sexual dysfunction in the older patients in this study, or to some other unidentified study-related factor.

Overall, the sexual adverse events data identified in the Gormley, Grino, Nickel, and Whiting studies in men 41 to 60 do not warrant inclusion in the labeling, beyond the adverse events that are already included. The provided studies did not identify a new safety concern with finasteride, 1 mg and 5 mg, for benign prostatic hyperplasia that warrants labeling updates. The known sexual adverse events are already included in the current labeling. The studies in men with BPH and androgenic alopecia did not identify any new sexual adverse events specific to men 41 to 60 years old to warrant any change or addition in labeling.

You request that information be added to ADVERSE REACTIONS (Clinical Trials Experience) that describes the significant increase in penis disorders, testicular pain, breast enlargement, and breast tenderness in men taking finasteride in PLESS. You assert that PLESS supports adding penis disorders to the labeling because of the significant increases in penis disorder adverse events (p=0.041) in finasteride patients. You state that penis disorders occurred in 15 (1.0%) of finasteride patients versus 5 (0.3%) of placebo patients. The most common penis disorders in patients taking finasteride were curvature of the penis (4 patients) and decreased penile sensation (5 patients). The investigators considered the adverse event to be drug-related in 8 of the 15 finasteride-treated patients, whereas the adverse event was considered drug-related in 1 of the 5 placebo patients. You also assert that there were significant increases in testicular pain adverse events (p=0.018) in finasteride patients. In addition, you note the significant increases in breast enlargement adverse events (p=0.03) and breast tenderness adverse events (p=0.03) in finasteride

[108] Whiting D et al., Efficacy and Tolerability of Finasteride 1 mg in Men Aged 41 to 60 Years With Male Pattern Hair Loss, Eur J Derm (2003), Vol. 13, pp. 150-160.

patients. You state that breast enlargement and tenderness are estrogenic effects of finasteride.

We found a number of shortcomings of PLESS regarding penis disorders and testicular pain: (1) the numbers of such events are small, and the statistical significance between the two groups is lost when assessed using the investigator's determination of causality; (2) the numbers of individual specific penile disorder adverse events are very small, and differences between groups may be due to chance alone; (3) the risk of chance alone being responsible for these findings is evidenced by the result for penile pain, which is statistically worse for placebo; and (4) PLESS was conducted using finasteride, 5 mg, in an older, BPH population, with known predisposition to erectile dysfunction and other age-related sexual adverse experiences. Additionally, we could not find any supporting information in the PLESS results or elsewhere in your Petition for including significant increases in breast enlargement or breast tenderness in the ADVERSE REACTIONS (Clinical Trials Experience) section of labeling. Therefore, we have determined that the current labeling is accurate and sufficient. The labeling includes in the ADVERSE REACTIONS (Clinical Trial Experience) section a description of PLESS and a list of all conditions considered possibly, probably, or definitely drug-related by the investigator, for which the incidence of these adverse events occurring while using Proscar was ≥1% and greater than placebo over the 4 years of the study, including impotence, decreased libido, decreased volume of ejaculate, ejaculation disorder, breast enlargement, breast tenderness, and rash.

ii. ADVERSE REACTIONS (Postmarketing Experience)

You request that FDA require Organon to remove the sentence about the voluntary reporting of adverse reactions being insufficient to establish a causal relationship between the reaction and the drug product. You did not provide support for this request in your Petition. Information in the ADVERSE REACTIONS (Postmarketing Experience) section of the Propecia labeling is from voluntary reports from a population of uncertain size. This sentence in the labeling helps health care practitioners interpret the significance of the data obtained from postmarketing spontaneous reports on finasteride. Accordingly, we deny your request to remove this sentence from the Propecia labeling.

You argue that the ADVERSE REACTIONS (Postmarketing Experience) section of the Propecia labeling should be updated to state that male infertility, spermatogenic failure, and/or poor seminal quality continued after the discontinuation of treatment with finasteride.

The Merck studies 056 and 012 were submitted as part of the original NDA, and the results of these studies do not necessitate labeling changes to the ADVERSE REACTIONS (Postmarketing Experience) section of the labeling. The ADVERSE REACTIONS (Postmarketing Experience) section does not include data from clinical trials. Additionally, section III.A.2.a. of this response describes FDA's findings with respect to these studies. In sum, Merck Study 056 affirmed the reduced ejaculate volume effect of finasteride. Data from this study demonstrating a statistically significant reversible reduction in ejaculate volume related to treatment with 5 mg of finasteride as compared to placebo are already included in the Propecia labeling. Merck Study 012 did not confirm a statistically significant difference in total sperm per ejaculate or percentage motile sperm between the drug and placebo groups, and there is no related reportable finding to include

in the labeling.

You also cite a study by Amory et al. (2007), which assessed testosterone, DHT, and semen parameters for 99 healthy male subjects aged 18 to 55 who received treatment with dutasteride, 0.6 mg; finasteride, 5 mg; or placebo for 1 year.[109] Statistically significant differences between finasteride and placebo were observed at week 26, but not at week 52, for total sperm count, semen volume, and sperm concentration. For these sperm parameters, differences between groups were not observed at follow-up after drug discontinuation. The author states that "the clinical significance of this small decrease (approximately 10%) is unclear and may be minimal." Furthermore, the study authors note that the impact of finasteride on fertility is unknown because average sperm concentrations decreased only slightly and remained above 20 million/milliliter (mL), the lower limit of the normal reference range, based on the 4th edition of World Health Organization (WHO) laboratory manual for the examination and processing of human semen (WHO, 1999). The lower limit of the normal reference range for sperm concentration has since been further reduced, to 15 million/mL, as described in the 5th edition of the WHO manual (WHO, 2010). In the Amory study, finasteride, 5 mg, was associated with mild decreases in ejaculate volume, total sperm count ejaculate, and sperm concentration, but these parameters were reversible after drug discontinuation.

We also reviewed the epidemiological and observational studies cited in your Petition assessing spermatogenic failure and/or poor seminal quality that continued after discontinuation of treatment, and we conducted an independent literature review.[110] Pallotti (2020), Samplaski (2013), and Irwig (2014) are single-arm observational studies. The Pallotti study did not directly assess persistence of male infertility, spermatogenic failure, or seminal quality following discontinuation of finasteride. The Samplaski study was a retrospective analysis, did not collect samples on all subjects before treatment with finasteride, and did not account for potential confounding. The Irwig study was flawed, because it lacked baseline semen analyses and serum androgens and single semen samples in the majority of patients. Further, the Irwig study found no evidence to suggest the persistence of male infertility, spermatogenic failure, or poor seminal quality following discontinuation of finasteride treatment.

To further address your claim that spermatogenic failure and/or poor seminal quality continued after discontinuation of treatment, FDA conducted a broad independent FAERS search. We identified a total of 210 spontaneous postmarketing reports focusing on male infertility, spermatogenic failure, or poor seminal quality reported with finasteride use. Out of the 210 reports identified, 102 were litigation reports;[111] 28 were duplicate reports; 28 lacked outcome measures of any adverse event of interest after discontinuation of finasteride; 22 lacked sufficient

[109] Amory, J et al., The Effect of 5α-Reductase Inhibition With Dutasteride and Finasteride on Semen Parameters and Serum Hormones in Healthy Men, J Clin Endocrinol Metab (2007), Vol. 92, pp. 1659-1665.
[110] Pallotti F et al., Androgenetic Alopecia: Effects of Oral Finasteride on Hormone Profile, Reproduction and Sexual Function, Endocrine (2020), Vol. 68, pp. 688-694; Samplaski MK et al., Finasteride Use in the Male Infertility Population: Effects on Semen and Hormone Parameters, Fertil Steril (2013), Vol. 100(6), pp. 1542-1546; Irwig MS, Androgen Levels and Semen Parameters Among Former Users of Finasteride With Persistent Sexual Adverse Events, JAMA Dermatol (2014), Vol. 150(12), pp.1361-1363.
[111] The litigation cases generally did not provide information on the patients' fertility status prior to finasteride use and the temporal relationship of adverse event to drug use was often difficult to interpret.

information; 10 reported patients who continued finasteride or reported an adverse event unrelated to male infertility, spermatogenesis, or seminal quality; and 3 lacked patient-level data. After excluding these reports, we analyzed 17 cases, including 12 literature cases. Nine of the 17 cases reported recovery to normal or near normal seminal quality after finasteride discontinuation. We identified eight cases of persistent low motility, teratozoospermia, necrozoospermia, or sperm count below normal, and nine cases that reported recovery to normal or near normal seminal quality after finasteride discontinuation. The analysis of these FAERS reports did not suggest that there was persistence of male infertility, spermatogenic failure, or poor seminal quality after discontinuation of finasteride treatment.

Neither the literature references nor the limited number of postmarketing case reports cited in your Petition suggest that spermatogenic failure and/or poor seminal quality continued after discontinuation of treatment. In fact, randomized, controlled trials showed that changes in seminal parameters did resolve when finasteride treatment was discontinued. Additionally, these studies assessed the effects of finasteride, 5 mg, not finasteride, 1 mg, and any findings are of uncertain relevance to finasteride, 1 mg. The information in the ADVERSE REACTIONS (Postmarketing Experience) section of the Propecia labeling is sufficient and accurate, and accordingly, we deny your request require Organon to update the labeling to state that male infertility, spermatogenic failure, and/or poor seminal quality continued after the discontinuation of treatment with finasteride.

d. CLINICAL STUDIES

Your Petition requests that FDA require Organon to amend certain language in the CLINICAL STUDIES section (Studies in Men, Other Results in Vertex Baldness Studies) of the Propecia labeling. Specifically, you request that FDA require Organon to change the heading from "Other Results in Vertex Baldness Studies" to "Sexual Function Questionnaire." You also request that FDA require Organon to include the results for the domain *morning erections* in the results of the sexual function questionnaire. In addition, you request that we require Organon to move "[a]t Month 12, statistically significant differences in favor of placebo were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems)" from the CLINICAL STUDIES section of the labeling to ADVERSE REACTIONS (Clinical Trials Experience) (Petition at 5). You argue that this language is misleading because it is not clear that "statistically significant differences in favor of placebo" refers to the placebo or finasteride as resulting in worse sexual functioning. You argue that the CLINICAL STUDIES section (Studies in Men, Other Results in Vertex Baldness Studies) should be moved to the ADVERSE REACTIONS section of the Propecia labeling because antiandrogenic effects of finasteride directly cause the impairment of sexual function in men treated with finasteride.

We agree that the content under the Studies in Men, Other Results in Vertex Baldness part of the CLINICAL STUDIES section should be moved to the ADVERSE REACTIONS (Clinical Trials Experience) section of the Propecia labeling with the heading "Results from Sexual Function Questionnaire." The relocation of this information will facilitate a better prescriber understanding of the adverse reactions associated with this drug product and more thoroughly describe the clinical trials experience with respect to adverse reactions. However, we deny your

request require Organon to make the requested language change and add the results from the *morning erections* domain to the results from the sexual function questionnaire. Appropriate and clinically meaningful information is already conveyed in the labeling based on data from the questionnaire.

3. Proposed Labeling Changes With Respect to Clinical Pharmacology

a. CLINICAL PHARMACOLOGY

i. CLINICAL PHARMACOLOGY (Mechanism of Action)

You argue the CLINICAL PHARMACOLOGY (Mechanism of Action) section of the Propecia labeling is inadequate because you claim that additional information about all the steroid hormones metabolized by Type I and Type II 5α-reductase, and the Type I and Type II 5α-reductase metabolic pathways that synthesize neurosteroids, needs to be disclosed (Petition at 3). You conclude that this disclosure is important because the neurosteroids formed by the Type I and Type II 5α-reductase metabolic pathways are necessary for normal behavioral regulation and sexual function (Petition at 11). Currently, the finasteride product labeling specifies the effects of finasteride on the metabolism of testosterone into DHT by Type II 5α-reductase. You contend that the labeling does not describe how finasteride treatment results in a deficiency in testosterone, progesterone, androstenedione, epitestosterone, cortisol, cortisone, corticosterone, deoxycorticosterone, and aldosterone (Petition at 11).

You further assert that the Type II 5α-reductase isozyme is found in more tissues than is mentioned in the current labeling for finasteride (Petition at 13). The current labeling states, "[t]he Type II 5α-reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver." You request that labeling for finasteride enumerate the following tissues where Type II 5α-reductase is present:

> (i) genital skin and organs in humans, (ii) the spermatogonia, seminiferous tubules and Sertoli cells of the testes in humans, (iii) the cerebral cortex, hypothalamus and pituitary gland of the brain in humans, (iv) the penis and spinal cord in rats, and (v) the nucleus accumbens, amygdala, hippocampus, cerebellum and locus coeruleus of the brain in rats.

(Petition at 13-14).

It is your position that the presence of Type II 5α-reductase in these additional tissues is noteworthy because the presence of Type II 5α-reductase affects the synthesis and metabolization of the androgens in these tissues (Petition at 14). And therefore, your Petition states, tissues that are expected to be adversely affected by finasteride treatment are where androgen receptors are concentrated (Petition at 15).

The literature references you submitted in your Petition provide information on the immunohistochemical localization of human Type II 5α-reductase isozyme, and the data is

supported by semi-quantitative evidence on degree of immunoreactivity.[112] In general, there is evidence suggesting moderate to strong immunoreactivity in prostate, seminal vesicles, epididymis, hair follicles, and liver. Furthermore, additional literature evidence using immunoblotting technique showed the presence of Type II 5α-reductase isozyme in prostate, seminal vesicles, liver, and epididymis. These tissues are already included in the approved labeling. Although there is some evidence that Type II 5α-reductase isozyme is present in other tissues, the immunoreactivity data implied that it was generally mild to moderate. Additionally, all the tissues showing clear immunoreactivity that strongly indicate the presence of Type II 5α-reductase isozyme are already included in the labeling.

The approved labeling language states that, "[t]he Type II 5α-reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles, as well as liver." The term "primarily" suggests that the presence of Type II 5α-reductase isozyme is not restricted to the tissues listed in the Propecia labeling, and there is a possibility that the Type II 5α-reductase isozyme is present in the tissues not currently enumerated in the labeling. The labeling is not designed to provide an exhaustive list of all the tissues where the Type II 5α-reductase isozyme is present; rather, it is designed to include tissues that are most relevant to drug activity and may also include tissues where the Type II isozyme is primarily found.

Although there is some evidence using immunohistochemistry[113] about presence of Type II 5α-reductase isozyme in several other tissues in humans, only prostrate (basal cells), epididymis (basal cells), skin (hair follicle), epididymis (basal cells), and hair follicle (inner root sheath) have strong immunoreactivity for 5α-reductase isozyme.[114]

Another study found Type II isozyme among postnatal tissues by immunoblotting in the liver, prostate, seminal vesicle, and epididymis only, which is consistent with the tissues currently listed in the Propecia labeling.[115] Also, the labeling clearly states that "[t]he Type II 5α-reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver." Therefore, the labeling acknowledges the possibility that Type II 5α-reductase isozyme is present in other tissues, but it only lists those tissues where Type II 5α-reductase isozyme is primarily found.

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[112] Thigpen AE et al., Tissue Distribution and Ontogeny of Steroid 5α-Reductase Activity, J Clin Invest (1993), Vol. 92, pp. 903-910; Eicheler W et al., Immunocytochemical Localization of 5 Alpha-Reductase 2 With Polyclonal Antibodies in Androgen Target and Non-Target Human Tissues, J Histochem Cytochem (1994), Vol. 42(5), pp. 667-675; Aumuller G et al., Immunocytochemical Evidence for Differential Subcellular Localization of 5α-Reductase Isoenzymes in Human Tissues (1996), pp. 241-252; Celotti F et al., Steroid Metabolism in the Mammalian Brain: 5α-Reduction and Aromatization, Brain Res Bull (1997), Vol. 44(4), pp. 365-375; McPhaul M, Defects of Androgen Action (2006), pp 466-472.

[113] Immunohistochemistry is a method for detecting antigens or haptens in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissues.

[114] Aumuller G et al., Immunocytochemical Evidence for Differential Subcellular Localization of 5α-Reductase Isoenzymes in Human Tissues (1996), pp. 241-252; Eicheler W et al., Immunocytochemical Localization of 5 Alpha-Reductase 2 with Polyclonal Antibodies in Androgen Target and Non-Target Human Tissues, J Histochem Cytochem (1994), Vol. 42(5), pp. 667-675.

[115] Thigpen AE et al., Tissue Distribution and Ontogeny of Steroid 5α-Reductase Activity, J Clin Invest (1993), Vol. 92, pp. 903-910.

You request that the statement "Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into DHT" be corrected to reflect your view that finasteride is a selective, but not specific, inhibitor of Type II 5α-reductase (Petition at 4). You assert that studies show that finasteride inhibits Type II 5α-reductase and Type I 5α-reductase, but with more selectivity towards Type II.[116] You argue that the labeling should disclose the lack of selectivity because the androgens that are inhibited by 5α-reductase (both Type I and Type II) play a major role in sexual function and that current labeling does not adequately describe the risks to sexual function.

Specificity is used to describe the capacity of a drug to cause a particular action in a population. For example, a drug of absolute specificity of action might decrease or increase a specific function of a given gene or protein or cell type, but it must do one or the other, not both. Drugs with specific action bind directly to the receptor to produce a response. *Selectivity* is used to describe the ability of a drug to affect a particular population, i.e., gene, protein, signaling pathway, or cell, in preference to others.[117] For example, a selective drug would have the ability to discriminate between cell populations, and so affect only one cell population, and thereby produce an event. Selective drugs bind to only one target, and never any other targets, to produce a response.

The current language in the approved Propecia labeling clearly states that the mechanism of action of finasteride is based on its preferential inhibition of the Type II 5α-reductase isozyme, suggesting that finasteride also has other effects. For example, finasteride inhibits Type I isozyme and Type III isozyme.[118] The labeling also clearly states that in vitro binding studies using native tissues (scalp and prostate) that examined the potential of finasteride to inhibit either Type II 5α-reductase isozyme showed that it is 100-times more likely to bind to Type II (IC_{50} = 4.2 nanometers (nM)) 5α-reductase over Type I isozyme (IC_{50} = 500 nM). Therefore, finasteride prefers binding to the Type II isozyme and signifies that it is a specific inhibitor, rather than selective.

The approved labeling further states that the turnover for the enzyme-complex is approximately 30 days for Type II versus 14 days for Type I, which supports the longevity of enzyme-complex with Type II. This turnover rate indicates a preference towards inhibition of the Type II 5α-reductase isozyme as compared to Type I, and therefore reinforces the use of the term specific in

[116] Tian G et al., 17β-(N-tert-Butylcarbamoyl)-4-aza-5α-androstan-1-en-3-one is an Active Site-Directed Slow Time-Dependent Inhibitor of Human Steroid 5α-Reductase 1, Biochemisty (1994), Vol. 33, pp. 91-96; Bull H et al., Mechanism-Based Inhibition of Human Steroid 5α-Reductase by Finasteride: Enzyme-Catalyzed Formation of NADP-Dihydrofinasteride, a Potent Bisubstrate Analog Inhibitor, J Am Chem Soc (1996), Vol.118(10), pp. 2359-2365; Bull H and Harris G (Assignee: Merck & Co., Inc.), Irreversible Inhibition of Human 5α-Reductase, U.S. Patent No. 5,962,442 (October 5, 1999); Scolnick E, Testimony during Dermatologic and Ophthalmic Drugs Advisory Committee Meeting No. 48 (November 13, 1997); Yamana K et al., Human Type 3 5α-Reductase Is Expressed in Peripheral Tissues at Higher Levels Than Types 1 and 2 and Its Activity Is Potently Inhibited by Finasteride and Dutasteride, Horm Mol Biol Clin Investig (2010), Vol. 2(3), pp. 293-299.

[117] Mencher SK and Wang LG, Promiscuous Drugs Compared to Selective Drugs (Promiscuity Can Be a Virtue), BMC Clin Pharmacol. 2005.

[118] Yamana K et al., Human Type 3 5α-Reductase Is Expressed in Peripheral Tissues at Higher Levels Than Types 1 and 2 and Its Activity Is Potently Inhibited by Finasteride and Dutasteride, Horm Mol Biol Clin Investig (2010), Vol. 2(3), pp. 293-299.

the mechanism of action statement.

The references provided in your Petition support the use of the term *specific inhibitor* to describe finasteride in the CLINICAL PHARMACOLOGY (Mechanism of Action) section. Some relevant information from the literature is summarized below.

The information reflected in the current Propecia labeling is consistent with most of the articles you cite in your Petition. For example, the Bull and Harris (1999) article notes, "[a]lthough finasteride is not a significant inhibitor of human skin (Type 1) isozyme at doses employed in the treatment of BPH, finasteride does slowly form a comparable high affinity complex with this isozyme."[119] According to the Tian et al. (1994) article, the rate of formation of enzyme-complex with Type I isozyme is much slower than with Type II (prostate isozyme) enzyme-complex, and therefore reveals a *preference* for Type II.[120] Thus, the literature referenced in your Petition is consistent with the currently approved labeling.

Another article you cite by Bull et al. (1996) concluded that the rate constant of the Type I enzyme-complex with finasteride is much smaller (i.e., < 1%) than the rate constant of the Type II enzyme-complex.[121] The authors determined that "[t]his rate constant contributes to making finasteride a more effective inhibitor of the type 2 than the type 1 isozyme in vivo, since it dictates the concentration of inhibitor required to influence steady-state pools of each isozyme."[122] You also cite in your Petition the article by Tian et al. (1994), which notes that "[t]his means that it takes 70 times longer for finasteride to completely inhibit 5α-reductase I than to inhibit 5α-reductase II."[123] In addition, the Yamana et al. (2010) article you reference shows that finasteride inhibits 5α-reductase II (IC_{50} =14.3 micrometers (μM)) and 5α-reductase III (IC_{50} =17.4 μM) with similar potency and with a 7.5-fold greater potency than 5α-reductase I (IC_{50} =106.9 μM).[124]

Based on the totality of evidence from the mechanism of action language in the approved labeling as well as the summary of literature evidence discussed above, finasteride has a much greater preference toward inhibition of Type II 5α-reductase isozyme compared to Type I, and the turnover rate for the enzyme-complex for Type II is twice as high as the turnover rate for Type I. This information supports in principle that finasteride is a competitive and specific inhibitor of Type II 5α-reductase. The current approved labeling accurately describes the

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[119] Bull H and Harris G (Assignee: Merck & Co., Inc.), Irreversible Inhibition of Human 5α-Reductase, U.S. Patent No. 5,962,442 (October 5, 1999).
[120] Tian G et al., 17β-(N-tert-Butylcarbamoyl)-4-aza-5α-androstan-1-en-3-one is an Active Site-Directed Slow Time-Dependent Inhibitor of Human Steroid 5α-Reductase 1, Biochemistry (1994), Vol. 33, pp. 91-96.
[121] Bull H et al., Mechanism-Based Inhibition of Human Steroid 5α-Reductase by Finasteride: Enzyme-Catalyzed Formation of NADP-Dihydrofinasteride, a Potent Bisubstrate Analog Inhibitor, J Am Chem Soc (1996), Vol. 118(10), pp. 2359-2365.
[122] Id.
[123] Tian G et al., 17β-(N-tert-Butylcarbamoyl)-4-aza-5α-androstan-1-en-3-one is an Active Site-Directed Slow Time-Dependent Inhibitor of Human Steroid 5α-Reductase 1, Biochemistry (1994), Vol. 33, pp. 91-96.
[124] Yamana K et al., Human Type 3 5α-Reductase Is Expressed in Peripheral Tissues at Higher Levels Than Types 1 and 2 and Its Activity Is Potently Inhibited by Finasteride and Dutasteride, Horm Mol Biol Clin Investig (2010), Vol 2(3), pp. 293-299..

finasteride mechanism of action as a specific inhibitor, and changes to the labeling are not necessary.

You assert that the CLINICAL PHARMACOLOGY (Mechanism of Action) section of the Propecia labeling is misleading. You argue that the labeling does not disclose critically important information about the mechanism of action of Propecia. You state that additional information needs to be disclosed about all of the steroid hormones metabolized by 5α-reductase, Type I and Type II, and the 5α-reductase, Type I and Type II, metabolic pathways that synthesize neurosteroids. You suggest the addition of the following language to the labeling:

> The deficiency of 5α-reductase activity induced by finasteride is not specific for androgen metabolism, but is a general deficiency in steroid metabolism affecting C_{19} and C_{21} steroids, including testosterone, progesterone, glucocorticoids and aldosterone. Inhibition of Type I and II 5α-reductase isozymes reduces formation of biologically active metabolites and neuroactive steroids, including dihydrotestosterone, dihydroprogesterone, allopregnanolone, dihydrodeoxycorticosterone and tetrahydrodeoxycorticosterone.

(Petition at 3).

The CLINICAL PHARMACOLOGY (Mechanism of Action) section in labeling of a drug product is designed to describe the probable mechanism for drug action for the labeled indication. It is not designed to describe all mechanisms of drug activity outside the labeled indication. Accordingly, it would not be appropriate to include in this section of labeling all of the steroid hormones metabolized by 5α-reductase, Type I and Type II, and the 5α-reductase, Type I and Type II, metabolic pathways that synthesize neurosteroids. Therefore, we deny your request to enumerate each neurosteroid metabolized by 5α-reductase, Type I and Type II.

ii. CLINICAL PHARMACOLOGY (Pharmacodynamics)

The CLINICAL PHARMACOLOGY (Pharmacodynamics) section of current finasteride labeling states that finasteride has "no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects." You argue that this statement is misleading because it refers to the lack of intrinsic hormonal activity of finasteride, but it does not account for finasteride competing with testosterone for binding sites on the 5α-reductase enzyme, which is an antiandrogenic activity (Petition at 36). You present several articles to support your proposition that the androgen inhibiting effects of finasteride are akin to antiandrogenic effects because of the reduction in serum dihydrotestosterone levels regardless of the dosage of finasteride taken (Petition at 36). You argue that finasteride has antiandrogenic and estrogenic effects, and therefore the labeling is misleading. You request that antiandrogenic and estrogenic be removed from the list of effects of finasteride so that the labeling reads, "[f]inasteride has no affinity for the androgen receptor and has no androgenic, antiestrogenic or progestational effects" (Petition at 4).

Estrogenic effects are exerted by binding to specific estrogen receptors, and similarly, androgens

exert their effects by binding to the androgen receptors. Estrogen-regulated and androgen-regulated gene expression are critical for the development and maintenance of female and male sexual phenotypes.

Finasteride is a competitive and specific inhibitor of the Type II 5α-reductase isozyme, which converts the androgen testosterone into DHT. Finasteride exerts its action by inhibiting Type II 5α-reductase and not via binding to any specific receptors. DHT is one of the androgens responsible for the development of male sexual organs and sexual function. The approved Propecia labeling clearly states that finasteride has no affinity for the androgen receptors. The fact that finasteride does not directly bind to the androgen receptors supports the fact that finasteride is not expected to have any androgenic, antiandrogenic, estrogenic, antiestrogenic, or pregestational effects from a mechanistic standpoint, because sex hormones exert their effects via specific receptor binding. Also, in vitro data supports the finding of a lack of any receptor binding of finasteride. As observed in studies, finasteride did not have any clinically meaningful changes in luteinizing hormone (LH), follicle-stimulating hormone, or prolactin.[125] Furthermore, the approximately 15 percent increase in the levels of testosterone and estradiol was deemed to be within the normal physiologic range, and the totality of this information does not provide reasonable evidence to support removal of the statement from the labeling indicating that finasteride has no antiandrogenic and estrogenic effects.

The probability of observing any antiandrogenic and estrogenic effects due to finasteride cannot be mechanistically explained with accuracy. Any clinical manifestations to suggest plausible antiandrogenic and estrogenic effects observed during treatment with finasteride are included in the ADVERSE REACTIONS section of the labeling. Your proposal to remove the statement that finasteride does not have any antiandrogenic and estrogenic effects from the CLINICAL PHARMACOLOGY (Pharmacodynamics) section of labeling is not appropriate. However, based on our analysis of the information contained in part and prompted by your Petition, FDA will require that Organon update the Propecia labeling to include the following sentence to describe the relationship between the mechanistic and clinical hormonal effects of finasteride:

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[125] Kuhn J et al., Effects of 10 Days Administration of Percutaneous Dihydrotestosterone on the Pituitary-Testicular Axis in Normal Men, J Clin Endocrinol Metab (1984), Vol. 58, pp. 231-235; Gormley GJ et al., The Effect of Finasteride in Men With Benign Prostatic Hyperplasia, N Engl J Med (1992), pp. 1185-1191; Rittmaster R et al., Effect of Finasteride, A 5α-Reductase Inhibitor, on Serum Gonadotropins in Normal Men, J Clin Endocrinol Metab (1992), Vol. 75, pp. 484-488; Grino P et al., Finasteride for the Treatment and Control of Benign Prostatic Hyperplasia: Summary of Phase III Controlled Studies, Eur Urol (1994), Vol. 25 (supplement), pp. 24-28; Canovatchel W et al., LH Pulsatility in Subjects With 5α-Reductase Deficiency and Decreased Dihydrotestosterone Production, J Clin Endocrinol Metab (1994), Vol. 78, pp. 916-921; Andriole G et al., Treatment With Finasteride Following Radical Prostatectomy for Prostate Cancer, Urology (1995), Vol. 45(3), pp. 491-497; Castro-Magana M et al., Effect of Finasteride on Human Testicular Steroidogenesis, J Androl (1996), Vol. 17(5), pp. 516-521; Roberts J, Clinical Dose Ranging Studies With Finasteride, Type 2 5α-Reductase Inhibitor, in Men With Male Pattern Hair Loss, J Amer Acad Derm (1999), Vol. 41, pp. 555-563; Overstreet J et al., Chronic Treatment With Finasteride Daily Does Not Affect Spermatogenesis or Semen Production in Young Men, J Urology (1999), Vol. 162, pp. 1295-1300; Kaufman K et al., Finasteride in the Treatment of Men With Androgenetic Alopecia, J Amer Acad Derm (1998), Vol. 39, pp. 578-589; Poletti A et al., 5α-Reductase Type 2 and Androgen Receptor Expression in Gonadotropin Releasing Hormone GT1-1 Cells, J Neuroendocrinol (2001), Vol. 13, pp. 353-357; Shakil T et al., Differential Regulation of Gonadotropin-Releasing Hormone Secretion and Gene Expression by Androgen: Membrane Versus Nuclear Receptor Activation, Molec Endocrinol (2002), Vol. 16, pp. 2592-2602.

"[t]he relationship between these pharmacodynamic activities and the mechanisms(s) by which Propecia exerts its clinical effect is unknown."

The CLINICAL PHARMACOLOGY (Pharmacodynamics) section of the current finasteride labeling states that therapy with finasteride does not produce clinically meaningful changes in LH levels. You argue that this labeling is incorrect because significant increases in LH have been reported in studies with finasteride, 1 mg, in men with benign prostatic hyperplasia (Petition at 105). You state that the study FDA relies on to assert that there were not significant changes in LH in men with androgenic alopecia who were treated with finasteride, 1 mg, is flawed (Petition at 105). Therefore, you argue that the labeling should be updated to reflect the clinically meaningful difference in LH levels.

As reflected in the currently approved Propecia labeling, treatment with finasteride in healthy subjects did not alter the response of LH and follicle-stimulating hormone to gonadotropin-releasing hormone. Therefore, the hypothalamic-pituitary-testicular axis was not affected by treatment with finasteride. The information that you are proposing to add also suggests that there was no change in LH in subjects with androgenic alopecia following treatment with a 1 mg dose of finasteride, and this information is already in the Propecia labeling.

4. Requested Risk Evaluation and Mitigation Strategy for Propecia

Your Petition requests that FDA send Organon a notification letter of the need for a REMS for Propecia. You request that the REMS include a requirement that Organon send a Dear Health Care Provider Letter to dermatologists, hair restoration surgeons, internists, family practitioners, psychiatrists, psychologists, urologists, and endocrinologists to inform these providers that Propecia has serious adverse reactions associated with its use and poses a significant public health concern. You also request that Organon develop a Medication Guide and Communication Plan to inform patients that Propecia has serious risks relative to benefits that may affect a patient's decision to use or continue to use Propecia (Petition at 2).

A REMS is not necessary to ensure the benefits of Propecia and generic versions of Propecia, 1 mg, outweigh its risks. We would add a REMS when labeling is not adequate to ensure the benefits outweigh the risks. The current labeling, with the changes we are requiring under section 505(o)(4) of the FD&C Act, adequately ensures the benefits outweigh the risks for the use of Propecia in the treatment of androgenic alopecia. The adverse events, including persistent sexual dysfunction, infertility, depression, and suicidal ideation/behavior, are adequately and appropriately reflected in Propecia's labeling.

However, because we agree that patients should be made aware of certain sexual adverse reactions with Propecia, we are requiring that Organon change Propecia labeling to add sexual adverse events mentioned in the ADVERSE REACTIONS (Clinical Trials Experience) section to PATIENT COUNSELING INFORMATION. According to the ADVERSE REACTIONS (Clinical Trials Experience) section of the Propecia labeling, these sexual adverse events, reported in less than 2% of subjects in clinical trials, were the most frequently reported adverse events assessed as drug-related. According to the FDA Guidance for industry: *Patient*

Counseling Information Section of Labeling for Human Prescription Drugs and Biological Products – Content and Format, information in the PATIENT COUNSELING INFORMATION section typically focuses on the major risks of the drug, including risks that are "serious or otherwise clinically significant." We are therefore requiring that the following reactions be added to the PATIENT COUNSELING INFORMATION section of Propecia labeling: decreased libido, erectile dysfunction, and ejaculation disorder, including decreased ejaculate volume.

B. Removal of Propecia From the Market

Your Petition requests that FDA require the immediate removal of Propecia and generic versions of Propecia, 1 mg, from the market. You contend that Propecia should be removed from the market because it has "life-altering adverse drug reactions" that lead to severe and permanent disability or death (Petition at 119). You assert that Propecia is a cosmetic drug that does not treat a medical condition, and therefore that the potential serious risks against the limited benefit should mandate its immediate removal from the market to protect the public health (Petition at 119).

For the reasons discussed above, the safety concerns you present are not supported by reasonable evidence of a new risk that would change FDA's benefit/risk assessment and thus do not warrant removal of Propecia from the market. There is not reasonable evidence to support a causal association between the adverse events you name in your Petition and the 1 mg dose of finasteride. You cite literature to support the claim that Propecia negatively impacts sexual function and contributes to neuropsychological adverse effects, but that literature contains many significant deficiencies, as noted above in this response, which limit the interpretation of the findings.

You claim there is a risk of persistent or permanent erectile dysfunction following treatment with Propecia that would warrant removal of this product from the market. FDA shall withdraw approval of a drug product if it finds that "new evidence of clinical experience, not contained in [the] application or not available to the Agency until after such application was approved . . . evaluated together with the evidence available to the Agency when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved."[126] We carefully reviewed the evidence you submitted, including observational studies, meta-analyses, systematic reviews, case reports, and randomized controlled studies you submitted. Results from the randomized controlled trials referenced in your Petition, which are generally considered the strongest level of evidence, fail to demonstrate a causal relationship between finasteride use and persistent and permanent erectile dysfunction. We also reviewed the observational epidemiologic studies and conducted a FAERS search and conclude that none of the reviewed studies or the reviewed FAERS cases provide reasonable evidence supporting a causal association between finasteride and persistent sexual dysfunction. The observational epidemiologic studies were low quality due to small sample size, poor statistical methods, uncontrolled confounders, and significant bias.[127] In addition, the animal

[126] Section 505(e)(1) and (2) of the FD&C Act.
[127] See III.A.2.a.i. for a discussion of the studies; See also footnote 67.

studies provided to support this claim do not translate to humans.[128] We did not find that the evidence you submitted regarding persistent and permanent erectile dysfunction support a finding that Propecia is not safe for use under the conditions of use that were the basis for the approval.

The literature references you submitted with respect to male fertility and spermatogenesis contain flawed study methodology and do not support a finding that Propecia is unsafe for use under the conditions of use that were the basis for the approval. Additionally, after conducting an additional FAERS search to identify postmarketing spontaneous cases focusing on male infertility, spermatogenic failure, or poor seminal quality associated with Propecia use, we did not find support for a finding that Propecia is unsafe for use under the conditions of use that were the basis for the approval. And the animal studies you reference were exploratory and were not clinically relevant.

As discussed above, we conclude that the totality of the evidence of the association between depression and suicidal ideation/belief and Propecia, including case reports, observational studies, spontaneous postmarketing adverse event database analyses, and FAERS cases, do not support a finding that Propecia is unsafe for use under the conditions of use that were the basis for approval. In addition to the deficiencies identified in the literature you provided, it was challenging to interpret the clinical data because known negative psychosocial impact of androgenic alopecia itself may have contributed to the psychiatric events in many of the cases.[129]

We do not agree with your Petition that the evidence you submitted supports a finding that Propecia is unsafe for use under the conditions that were the basis for approval. The evidence that you provide in your Petition does not provide reasonable evidence of a causal association between Propecia use and persistent erectile dysfunction, male infertility, decreased spermatogenesis, depression, or suicidal ideation and behavior, and does not warrant additions to the WARNINGS AND PRECAUTIONS sections of the labeling or any language modifications on these topics. The evidence that you provide in your Petition does not support a finding that men with sexual dysfunction, depression, or male infertility should not be prescribed Propecia because the risks outweigh the benefits in these populations, and therefore does not warrant changes to the CONTRAINDICATIONS sections of labeling. Therefore, we have determined that removal of Propecia from the market is also not supported because Propecia is safe for use under the conditions of use that were the basis for approval, and we deny your request to remove Propecia from the market.

C. Requested Labeling Changes to Proscar

1. WARNINGS AND PRECAUTIONS, CONTRAINICATIONS, and BOXED WARNING

Your Petition requests that FDA require Organon to add to the WARNINGS AND

[128] See III.A.2.a.i. for a discussion of the studies; see also footnotes 80, 81, and 82.
[129] Cash TF, The Psychosocial Consequences of Androgenetic Alopecia: A Review of the Research Literature, Br J Dermatol. (1999), Vol. 141(3), pp. 398-405.

PRECAUTIONS, BOXED WARNING, and CONTRAINDICATIONS sections of Proscar labeling (NDA 020180) (and generic versions of Proscar, 5 mg) that the 5 mg finasteride tablet should not be split into quarters for the treatment of androgenic alopecia.

In regard to your concern that Proscar tablets could be split, broken, or crushed to produce smaller dosages, that concern is already included in current labeling, in the context of the potential risk to pregnant women who handle broken or crushed Proscar tablets and is not specific to off-label treatment of androgenic alopecia in men. Proscar labeling states that Proscar is for the treatment of symptomatic BPH in men with an enlarged prostate. You have not provided evidence that splitting Proscar tablets leads to serious/clinically significant adverse reactions that have implications when prescribing for or managing men being treated for BPH, the approved use for Proscar. A BOXED WARNING further highlights a particular WARNING AND PRECAUTION and is used when there is "an adverse reaction, so serious in proportion to the potential benefit from the drug (e.g., fatal, life-threatening, permanently disabling) that it is essential that it be considered in assessing the risks and benefits of using the drug or there is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug."[130] There is no evidence that splitting Proscar tablets when treating men with BPH leads to serious reactions that would meet the criteria for a BOXED WARNING.

FDA may require additions to the WARNINGS AND PRECAUTIONS section of labeling for adverse reactions associated with an unapproved use if the drug is commonly prescribed for a disease or a condition and such usage is associated with a clinically significant risk or hazard. The WARNINGS AND PRECAUTIONS section would describe that safety and effectiveness have not been established in such a setting and that such use is not FDA-approved. This situation does not apply to your request in the Petition because finasteride is FDA-approved for treatment of androgenic alopecia.

The CONTRAINDICATIONS section of labeling must describe any situations in which the drug should not be used because the risk of use "clearly outweighs any possible therapeutic benefit."[131] A risk of Proscar use includes potential risk to pregnant women who handle broken or crushed Proscar tablets, which is clearly outlined in the WARNINGS AND PRECAUTIONS section of the Proscar labeling. These risks, however, do not qualify as a CONTRAINDICATION because there is a lack of evidence suggesting they are substantial or potentially fatal and that they could outweigh the therapeutic benefit of Proscar for the labeled use. Therefore, addition of instructions to not split Proscar into smaller dosages for the treatment of androgenic alopecia in the CONTRAINDICATIONS section is unwarranted. Your Petition does not provide specific information that supports new labeling, and we are not aware of any other new information that would support such new labeling. Therefore, we deny your request to include language in the Proscar label indicating that the 5 mg finasteride tablet should not be split into quarters for the treatment of androgenic alopecia.

2. ADVERSE REACTIONS (Clinical Trials Experience)

[130] See the Warnings Guidance, available at https://www.fda.gov/media/71866/download.
[131] § 201.57(c)(5).

Your Petition requests that FDA require Organon to delete the language in the ADVERSE REACTIONS (Clinical Trials Experience) section of the Proscar labeling that states, "There is no evidence of increased sexual adverse experiences with increased duration of treatment with PROSCAR 5 mg."

You cite three references that summarize the results of randomized, placebo-controlled studies but that do not provide evidence of increased sexual adverse experiences with a longer duration of treatment with Proscar.[132] Sexual adverse reactions did not appear to increase with increased duration of treatment. As noted in section III.A.2.a. of this response, the three observational study references have numerous study design deficiencies and limitations that preclude the use of these references to support your argument that there are increased sexual adverse experiences with longer duration of treatment with Proscar.[133]

IV. CONCLUSION

For the reasons explained above, your Petition is denied in part and granted in part. We are denying your requests, as enumerated above, for the additional information to be added to the WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, ADVERSE REACTIONS, CLINICAL PHARMACOLOGY, and BOXED WARNING sections of Propecia and Proscar labeling. We also deny your request to require Organon to implement a REMS, and we deny your request to remove Propecia from the market.

The totality of the evidence presented in your Petition does not provide reasonable evidence to support a causal association between Propecia use and persistent and permanent sexual dysfunction, male infertility or impaired spermatogenesis, depression, suicidal ideation/behavior, anxiety, cognitive dysfunction, and fatigue. The majority of your labeling change requests to the WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, ADVERSE REACTIONS, CLINICAL PHARMACOLOGY, and BOXED WARNING sections of labeling, including amending, deleting, and adding new information to the existing labeling, are not warranted. The literature you submitted fails to support your proposed labeling change requests due to study design flaws and limitations, such as retrospective, open label design, lack of baseline clinical assessment, missing clinical information and data, small sample size, use of non-validated clinical instruments, poor statistical methods, misclassification of exposure and/or outcomes,

[132] Stoner E et al., Maintenance of Clinical Efficacy With Finasteride Therapy for 24 Months in Patients With Benign Prostatic Hyperplasia, Arch Intern Med (1994), Vol. 154, pp. 83-88; Hudson P et al., Efficacy of Finasteride Is Maintained in Patients With Benign Prostatic Hyperplasia Treated for 5 Years, Urology (1999), Vol. 53, pp. 690-695; Waldstreicher J and Wang D, Finasteride (MK-906) Clinical Study Report Synopsis (July 31, 1997, revised August 19, 1997).

[133] Traish AM et al., Finasteride, Not Tamulosin, Increases Severity of Erectile Dysfunction and Decreases Testosterone Levels in Men With Benign Prostatic Hyperplasia, Horm Mol Biol Clin Invest (2015), Vol. 23(3), pp. 85-96; Traish AM et al., Adverse Side Effects of 5α-Reductase Inhibitors Therapy: Persistent Diminished Libido and Erectile Dysfunction and Depression in a Subset of Patients, J Sex Med (2011), Vol. 8, pp. 872-884; Kiguradze T, Persistent Erectile Dysfunction in Men Exposed to the 5α-Reductase Inhibitors Finasteride or Dutasteride, PeerJ (2017), Vol. 5, pp. 1-31.

recall bias, selection bias, reporting bias, lack of adjustment for confounders, and non-generalizability of data.

However, based on our analysis of the information contained in part and prompted by your Petition, we are requiring that Organon make labeling changes under section 505(o)(4) of the FD&C Act to clarify the risks of use of Propecia. We are requiring the addition of suicidal ideation and behavior to the list of nervous system/psychiatric reactions in the ADVERSE REACTIONS (Postmarketing Experience) section of the Propecia labeling. FDA is also requiring that Organon move the content under the "Other Results in Vertex Baldness" in the CLINICAL STUDIES section of the labeling to the ADVERSE REACTIONS (Clinical Trials Experience) section and change the title to "Results from Sexual Function Questionnaire." We are requiring that Organon change the Propecia labeling to add sexual adverse events mentioned in the ADVERSE REACTIONS (Clinical Trials Experience) section to PATIENT COUNSELING INFORMATION. We are requiring that the following reactions be added to the PATIENT COUNSELING INFORMATION section of the Propecia labeling: decreased libido, erectile dysfunction, and ejaculation disorder, including decreased ejaculate volume. Finally, FDA is requiring Organon to update the Propecia labeling to include the following sentence to describe the relationship between the mechanistic and clinical hormonal effects of finasteride: "[t]he relationship between these pharmacodynamic activities and the mechanisms(s) by which Propecia exerts its clinical effect is unknown."

We have informed Organon that it must change its labeling as set forth above.[134] With those changes, the Propecia labeling adequately describes the risk of sexual dysfunction and psychoneurocognitive adverse events with use of Propecia and upon drug discontinuation. As always, FDA will continue to monitor the safety data, including adverse event reports, for Propecia and Proscar, as we do with all drugs regulated by the Agency.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2022.06.08 16:49:06 -04'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[134] In accordance with section 505(o)(4), Organon has been notified that on or before June 30, 2022, they are required to submit a supplement proposing these changes or notify the agency that they do not think the changes are warranted and a statement detailing why. If Organon does not submit the required changes or the agency disagrees with alternative language proposed by the NDA holder, the FD&C Act provides timelines for discussions between FDA and Organon. At the conclusion of those discussions, FDA may issue an order directing Organon to make the changes, as appropriate.