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Peruvian Ministry of Health

RD No. 2076. 2018-DIGEMID/DPF/MINSA
DIRECTOR'S RESOLUTION
Lima, March 9, 2018

HAVING SEEN REPORT No. 012-2017-DIGEMID-DFAU-UFCENAFyT/MINSA of July 5, 2017, with internal file No. 17-056147-1, on safety for medications containing FINASTERIDE; CONSIDERING:

That finasteride is a specific inhibitor of 5a-reductase type II, an intracellular enzyme that metabolizes testosterone to convert it into a more potent androgen, 5a-dihydrotestosterone (DHT); which appears to be the main androgen responsible for the stimulation of prostate growth. Likewise, in the 1 mg dose it is indicated for the treatment of hair loss in men with androgenetic alopecia and in the 5 mg dose it is indicated for the treatment and control of Benign Prostatic Hyperplasia (BPH).

Finasteride is a synthetic compound that is a competitive inhibitor of the type II 5a-reductase enzyme, an enzyme present in high concentrations in the liver, skin, and prostate. The conversion of testosterone into the active metabolite 5a-dihydrotestosterone (DHT) depends on the presence of this enzyme. Finasteride is used to reduce prostate size, urinary obstruction and associated manifestations (eg, difficulty and/or urgency in urination, nocturia), risk of acute urinary retention, and risk of the need for surgery (including transurethral resection of the bladder, prostate and prostatectomy) in patients with symptomatic benign prostatic hyperplasia (Benign Prostatic Hypertrophy). Finasteride is also used orally to stimulate hair growth in men with mild to moderate androgenetic alopecia (male pattern baldness, hereditary alopecia, and male pattern baldness). The use of Finasteride is contraindicated in women who are or may be pregnant. If a pregnant woman receives the drug, it could cause abnormalities in the external genitalia of a male fetus, since finasteride inhibits the conversion of testosterone to dihydrotestosterone. In addition, pregnant women should not handle crushed or broken finasteride tablets, due to the possibility of absorption and subsequent risk to the male fetus;

That the UK's High Health Surveillance Regulatory Agency (MHRA) issued a statement noting that there have been reports of depression and, in rare cases, suicidal thoughts in male patients taking finasteride 1mg (Propecia) for male pattern hair loss. It also indicates that it should be noted that depression is also associated with finasteride 5 mg (Proscar). It also points out that the 1 mg dose of finasteride is indicated for the treatment of hair loss in men (androgenetic alopecia), and the 5 mg dose is indicated for the treatment and control of benign prostatic hyperplasia. The statement will note that some men have reported episodes of depressive illness in association with the use of Propecia used for male pattern hair loss, including some of them also reporting suicidal thoughts. Depression and suicidal thoughts have been reported in men with and without a prior history of depression. Depressive mood has been previously recognized with Propecia. A recent review of the evidence has suggested that a more significant depression may occur, for which an update is being made. It should be noted that the Proscar product information already lists depression as a possible adverse reaction and is being updated due to a recent review. Among the recommendations made by the MHRA, healthcare professionals are reminded that adverse reactions related to sexual function have been reported in association with the use of

finasteride. These include decreased libido, erectile dysfunction, and ejaculatory disorders (such as decreased volume of ejaculate);

That the European Medicines Agency (EMA) published the scientific conclusions referring to the evaluation of the Periodic Safety Reports (IPS) for Finasteride. The evaluation was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), which observed that during the reference period two serious cases were obtained for Finasteride 5 mg, one in which suicidal behavior was reported and in the other case suicidal ideation. Cumulatively, 51 cases of suicidal ideation have been obtained according to the information in the summary table of adverse drug reactions during post-marketing use. Taking into account the severe cases reported and that depression is already included in the Summary of Product Characteristics or Summary of Product Characteristics for finasteride 5 mg, the PRAC recommended including a warning in the SmPC for finasteride, to inform that mood disturbances, depression, and suicidal ideation have been reported. A recommendation to monitor patients and remind them to seek medical advice if they develop psychiatric symptoms should also be included. The coordination group for mutual recognition and decentralized procedures (GMDh) also considered the recommendation already given by the PRAG for finasteride 1 mg, indicated for the treatment of male-type hair loss. The PRAG considered that the changes in the technical data sheet were justified, so the holders of the marketing authorization for medicines containing 1 mg of finasteride indicated for the treatment of male-type hair loss, must align the information of their medicines with these recommendations. The GMDh agrees with the scientific conclusions of the PRAG. However, regarding the 1 mg dose, the GMDh considers that this change should be part of this single evaluation procedure. In accordance with the scientific conclusions for finasteride, the GMDh considers that the benefit-risk balance of medicines containing finasteride is not modified. The GMDh concludes that the marketing authorization of the drugs should be modified within the scope of the sole evaluation of this IPS. Likewise, for other medicines that contain finasteride and that are currently authorized in the European Union or that are going to be subject to future authorization procedures, the GMDh recommends that the member states and the Marketing Authorization Holders should take this position into account.

The GMDh indicates the modifications that must be included in the sections of the product information that contain:

Finasteride 5 mg:

Summary of Product Characteristics: Warnings Section: Mood and Depression Side Effects: Mood changes, including depressed mood, depression, and, less frequently, suicidal ideation have been reported in patients treated with finasteride 5 mg. Patients should be monitored for psychiatric symptoms and if these occur, the patient should be instructed to seek medical advice.

Package Insert

Warnings and Precautions Section: Mood and Depression After Effects: Mood disturbances, such as depressed mood, depression, and less frequently, suicidal ideation have been reported in patients treated with finasteride. If you experience any of these symptoms, see your doctor as soon as possible.

Finasteride 1 mg:

Summary of Product Characteristics: Warnings Section: Mood changes, including depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with finasteride 1mg. Patients should be monitored for psychiatric symptoms and if these occur, finasteride should be

discontinued and the patient instructed to seek medical advice. Adverse Reactions Section: add the adverse reaction “depression” in the system organ class in psychiatric disorders with a frequency of uncommon.

Package Insert: Warnings and Precautions Section: Mood Alterations and Depression: Mood alterations, such as depressed mood, depression, and less frequently, suicidal ideation have been reported in patients treated with finasteride. If you experience any of these symptoms, stop taking finasteride and see your doctor as soon as possible.

Adverse Reactions Section: add the adverse reaction “depression” with a frequency of uncommon;

That, a study published in the journal Pharmacotherapy in 2015, had the objective of evaluating persistent sexual dysfunction and suicidal ideation in young men treated with low doses of finasteride. Reports of adverse events (n=4910) related to low-dose finasteride in men aged 18-45 years were recorded in the FAERS (Food and Drug Administration Adverse Event Reporting System) database between the years 1998 and 2013. evaluation observed 577 (11.8%) reports of adverse events associated with persistent sexual dysfunction and 39 (7.9%) associated with suicidal thoughts, in patients who used low doses of finasteride. Of note, 34 of the 39 patients with suicidal thoughts also experienced persistent sexual dysfunction. Most of these events were serious (eg, contributed to the patient's death, hospitalization, or disability). The authors conclude by noting that persistent sexual dysfunction could be a potential risk of using low-dose finasteride for androgenetic alopecia in young men, and this risk may contribute to suicidal thinking. That, in our country, according to the consultation carried out in the SIDIGEMID database, to date, there are thirty (30) products that contain finasteride with the current health registration. The National Center for Pharmacovigilance and Technovigilance has received a total of 5 reports of suspected adverse reactions, among which are:

- Gastrointestinal disorders: constipation.
- Reproductive Disorders: impotence and pain in the chest (breasts).
- Skin Disorders: rash.
- Urinary Tract Disorders: kidney pain.

Being informed by the Directorate of Pharmacovigilance, Access and Use of this Institution;

With the endorsement of the Area of Efficacy, Safety and Quality and Area of Legal Advice of the Directorate of Pharmaceutical Products; and,

In accordance with Supreme Decree No. 016-2011-SA and its amendments, Supreme Decree No. 008-2017-SA and amendments, Law No. 29459 Law on Pharmaceutical Products, Medical Devices and Health Products, Legislative Decree No. 1161, Legislative Decree that approves the Organization and Functions Law of the Ministry of Health, Law No. 27444, Law of General Administrative Procedure and amendments, TUO of Law No. 27444, approved by Supreme Decree No. 006-2017-JUS;

RESOLVED:

Article 1.- Provide that the holders of the Sanitary Registries of current medications containing Finasteride, authorized before the entry into force of the TUPA approved with Supreme Decree No. 001-2016-SA and amendments, must include in the insert the following sections:

1. Add the following information in the medicines that contain finasteride 5 mg, in the sections:
• Warnings:
✓ Alterations of mood and depression:

Mood disturbances, including depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with finasteride 5 mg. Patients should be monitored for psychiatric symptoms and if these occur, the patient should be instructed to seek medical advice.

2. Add the following information in the medicines that contain finasteride 1 mg, in the sections:

• Warnings:
✓ Alterations of mood and depression:

Mood disturbances, including depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with Finasteride 1 mg. Patients should be monitored for psychiatric symptoms and if these occur, finasteride should be discontinued, and the patient instructed to seek medical advice.

• Adverse reactions:
✓ Infrequently: Depression.

Article 2. Provide that the holders of the Sanitary Registries of the current pharmaceutical specialties that contain finasteride, authorized after the entry into force of the TUPA approved with Supreme Decree No. 001-2016-SA and amendments, must include in the record technical information as indicated in article 1 of this Directorial Resolution and in the insert the following information:

1. Add the following information in the medicines that contain Finasteride 5 mg, in the sections:
• Warnings and Cautions:
✓ Alterations of mood and depression.

Mood disturbances, such as depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with finasteride. If you experience any of these symptoms, see your doctor as soon as possible.

2. Add the following information in the medicines that contain Finasteride 1 mg, in the sections:
• Warnings and Cautions:
✓ Changes in Mood and Depression:

Mood disturbances, coma depressed mood, depression and less frequently, suicidal ideation have been reported in patients treated with finasteride. If you experience any of these symptoms, stop taking Finasteride and see your doctor as soon as possible.
• Adverse reactions:
✓ Uncommon: Depression.

Article 3. Provide that within a period not exceeding thirty (30) business days counted from the day following the publication of this Directorial Resolution at the electronic address http://www.digemid.minsa.gob.pe / of the DIGEMID Internet portal, the holders of sanitary registrations carry out the modifications indicated in articles 1 and 2, as appropriate. The insert and/or technical file

must be modified only with the required information, considering the rest of the information according to the last authorized.

Article 4. The updating of the inserts and/or technical data sheets in the sections indicated in articles 1 and 2 of the medicines that contain Finasteride, will be in accordance with the Technical Data Sheets updated by the regulatory agencies of countries with high health surveillance.

REGISTER, COMMUNICATE AND POST:

QF Ana Gabriela Silva Flor
Executive Director of Pharmaceutical Products
Ministry of Health