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Health Product InfoWatch

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REPORTING ADVERSE REACTIONS

Canada Vigilance Program

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HEALTH PRODUCTS MENTIONED IN THIS ISSUE

Pharmaceuticals and Biologics

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Other

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Unauthorized health product (Natrol DHEA 25 mg)

This monthly publication is intended primarily for healthcare professionals and includes information on pharmaceuticals, biologics, medical devices and natural health products. It provides a summary of key health product safety information published in the previous month by Health Canada, as well as a selection of new health product safety information meant to raise awareness. New information contained in this issue is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

Canada

MONTHLY RECAP OF HEALTH PRODUCT SAFETY INFORMATION

The following is a list of health product advisories as well as summaries of completed safety reviews published in November 2015 by Health Canada.

Abilify (aripiprazole tablets) and Abilify Maintena (aripiprazole for prolonged release injectable suspension) Information Update Summary Safety Review	This safety review evaluated the potential link between Abilify and Abilify Maintena and the risk of certain impulse control behaviours. Health Canada's review concluded that there is a link between the use of aripiprazole and a possible risk of pathological gambling or hypersexuality. The Canadian product monograph for both these products has been updated to advise of these risks. Health Canada has also communicated this information to Canadians.
Alveda Atropine Injection BP 0.4 mg/mL Health Product Risk Communication	One lot (lot number: 50187) of Atropine Injection BP 0.4 mg/mL (DIN 02094681) marketed and sold by Alveda Pharmaceuticals Inc. was recalled due to an incorrect barcode on the ampoule label. The barcode reads (01)00837641000591 which is the same barcode number on the ampoule label of Alveda Epinephrine Injection USP 1 mg/mL (DIN 02325225).
Avastin (bevacizumab) Summary Safety Review	This safety review evaluated the potential link between Avastin and the risk of vocal cord necrosis. Health Canada's review concluded that there was not enough evidence to support a link. Health Canada will continue to monitor this safety issue.
Foreign health products Foreign Product Alert	Various Ayurvedic medicinal products were found to contain high levels of heavy metals which may pose serious health risks. These products are not authorized for sale in Canada and have not been found in the Canadian marketplace but it is possible they may have been brought into the country by travellers or purchased over the Internet.
Holkira Pak (ombitasvir/ paritaprevir/ritonavir and dasabuvir) and Technivie (ombitasvir/paritaprevir/ ritonavir) Information Update	In response to new international safety information, Health Canada advised Canadians that it is working with the manufacturer of Holkira Pak and Technivie to update its Canadian product monographs to include new information regarding serious liver injury.
Primene 10% Amino Acid Solution, 250 mL Health Product Risk Communication	This update on Primene 10% solution replaces the information previously communicated by Baxter Corporation on April 21, 2015, regarding a compatibility issue between Primene and trace elements. Recent investigations conducted by Baxter indicated that, only after filtration, levels of particulate matter in 2 in 1 and 3 in 1 parenteral nutrition test solutions containing Primene admixed with trace elements were within USP limits for particulate matter.

Unauthorized health product (Dragon Power) Advisory	Dragon Power, an unauthorized product sold at The Herb Depot in Toronto, Ontario, was found to contain an undeclared prescription drug (sildenafil) that may pose a serious risk to the health of Canadians. The product may also have been sold bearing the Natural Product Number (NPN) 80025214, or under the names "Super Dragon Power" or "Dragon Power II".
Unauthorized health product (Natrol DHEA 25 mg) Advisory	Health Canada informed Canadians that an unauthorized health product, Natrol DHEA 25 mg, was being sold on amazon.ca for hormonal management. This product may pose a serious risk to the health of Canadians.
Votrient (pazopanib) Summary Safety Review	This safety review evaluated the potential link between Votrient and the risk of pericardial effusion. Health Canada's review concluded that there was not enough information to support a link. Health Canada has requested that the manufacturer continue to provide information on this safety issue, and will continue to monitor the situation.

NEW HEALTH PRODUCT SAFETY INFORMATION

The following topics have been selected to raise awareness and, in some cases, to stimulate reporting of similar adverse reactions.

REVIEW ARTICLE

Finasteride and suicidality

Key points

- From 1992 to January 31, 2015, Health Canada received 12 reports of suicidality suspected of being associated with the use of finasteride in Canada.
- The potential link between finasteride and suicidality has also been reported in the medical literature, including the persistence of symptoms after treatment discontinuation. However, evidence is limited at this time and is insufficient to confirm a link.

Finasteride is a type II 5 alpha-reductase inhibitor indicated for the treatment and control of benign prostatic hyperplasia (Proscar) and male pattern hair loss (Propecia).[1] The enzyme 5 alpha-reductase is involved in the transformation of a variety of endogenous steroids, including the metabolism of testosterone. Finasteride was first marketed in Canada in 1992 as Proscar (5 mg) and subsequently in 1998 as Propecia (1 mg).

As of January 31, 2015, Health Canada received 12 reports of suicidality suspected of being associated with finasteride use in Canada. The onset of events ranged from 4 days to several years. Patients were men, aged 22 to 67 (age was not reported in 2 cases); 6 patients were under 30 years old. Nine reports indicated that the patient was using finasteride at a lower dose or to treat hair loss, and 3 reported the use of finasteride (higher dose) to treat benign prostatic hyperplasia.

Of the 12 patients, 2 recovered while 6 had not yet recovered at the time of reporting. The outcome was not stated in 3 reports. The last case reported a completed suicide but a causal relationship between finasteride and suicidality could not be established as limited information was available. Overall, 5 of the 12 reports were unassessable due to the limited information provided. Detailed assessable cases are presented in Table 1.

Key points (continued)

- Healthcare professionals are encouraged to report to Health Canada any adverse reaction suspected of being associated with finasteride use.

The most compelling case reported to Health Canada (Table 1, no.1) described a patient feeling depressed and irritable one week after starting finasteride to treat hair loss; this eventually led to suicidal thoughts. He subsequently ceased the medication and after 3 days, he started to feel normal. He reported that the anxiety, depressed feelings and suicidal thoughts had completely disappeared shortly after discontinuation. The patient had no prior history of depression, and the report suggested that no other changes had occurred in his life at that time.

Table 1: Summary of detailed reports of suicidality suspected of being associated with the use of finasteride, submitted to Health Canada from date of marketing to January 31, 2015.*

Case	Patient age / sex	Adverse reaction (AR) reported	Other ARs reported	Product name and dose	Indication	Exposure at the time of the AR†	Concomitant health products/ additional information	Outcome
1	NA/M	Suicidal ideation	Anxiety, depression, insomnia, irritability, personality change	Propecia‡	Hair loss	1-2 weeks	NA / No history of depression	Resolved
2	55/M	Suicidal ideation	Apathy, crying, depression	Proscar 5 mg daily	Benign prostatic hyperplasia	2 weeks	Vardenafil, acetylsalicylic acid / No history of psychiatric problems	Resolved
3	NA/M	Suicide attempt	Aggression, anxiety, depression, mood swings	Propecia‡	NA	Approximately 6 months	NA	Not yet recovered
4	22/M	Suicide attempt	Erectile dysfunction, abnormal semen analysis	NA, 1 mg ‡	Hair loss	Approximately 2 years	NA	NA
5	51/M	Suicidal ideation	Anxiety, asthenia, depression, erectile dysfunction, female weight gain pattern, musculo-skeletal stiffness, loss of libido, testicular pain	NA, 5 mg ‡	Benign prostatic hyperplasia	Approximately 2 years	NA	NA
6	27/M	Suicidal ideation	Anxiety, depression, insomnia, irritability, loss of appetite, mental breakdowns	Sandoz Finasteride A 1 mg daily	Hair loss	38 days	NA	NA
7	24/M	Suicidal ideation	Decreased libido, erectile dysfunction, migraine, pain in testicle, vertigo	NA, 0.5 mg daily	NA	4 days	NA	Not yet recovered

Note: NA = not available.

***These data cannot be used to determine the incidence of adverse reactions (ARs) because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**

†Estimated from the beginning of treatment.

‡Daily dose not specified in the report.

Article citation: Health Canada. Finasteride and suicidal ideation. *Health Product InfoWatch* December 2015: page 3-6.

Suicidality in association with finasteride use has been recently reported in the literature, both at lower doses (to treat male pattern hair loss) and at higher doses (to treat benign prostatic hyperplasia).[2-5] Studies conducted in former users of finasteride (including young men who used low doses), have also described persistent adverse events such as sexual dysfunction and suicidality despite having discontinued the drug for a number of months.[4-9] The interaction between sexual dysfunction and depression is complex, as one may lead to the other. However, according to the literature, finasteride could affect brain function and trigger depression and suicidal ideation independently of sexual dysfunction. The blockade of 5 alpha-reductase by finasteride could reduce levels of neuroactive steroids, which may have an impact on psychological and cognitive outcomes, including mood, depression and overall well-being.

In addition, the medical literature has recently been referring to Post-Finasteride Syndrome (PFS) when describing persistent sexual, neurological, and physical adverse reactions in patients who have taken finasteride and discontinued the treatment.[8] The U.S. National Institutes of Health (NIH) recently added PFS to its list of genetic and rare diseases.[10] According to the NIH, studies are underway to better understand the safety profile of 5 alpha-reductase inhibitors with respect to adverse reactions (sexual dysfunction, breast outcomes, and depression) and their permanency.

In Canada, suicidal ideation is not listed in the Canadian product monographs (CPMs) for Proscar and Propecia,[1] as evidence is limited at this time and insufficient to confirm a link, but depression is listed in the Post-Market Adverse Drug Reactions section. This is similar to the situation in the United States[11] and Europe.[12] The possibility of persistent sexual dysfunction is also listed in the CPMs.[1]

Suicidal ideation is a serious clinical event and raising awareness among healthcare professionals and patients of this potential risk is important. Healthcare professionals are encouraged to report to Health Canada any case of suicidality or any other adverse reaction suspected of being associated with finasteride. Information such as the dose, treatment duration, indication, concomitant medications, comorbidities and/or other underlying conditions, and time to onset of the adverse reaction should be included where possible.

References

1. *Proscar, Propecia (finasteride)* [product monograph]. Kirkland (QC): Merck Canada Inc.; 2014.
2. Uddin S, Garg V, Nardone B, et al. Mood disorders and suicidal ideation associated with 5-α reductase inhibitors: A RADAR report [abstract 974]. *J Invest Dermatol* 2013;133(S1):S166.
3. Traish AM, Melcangi RC, Bortolato M, et al. Adverse effects of 5α-reductase inhibitors: what do we know, don't know, and need to know? *Rev Endocr Metab Disord* 2015 Aug 23. DOI: 10.1007/s11154-015-9319-y.
4. Ali AK, Heran BS, Etminan M. Persistent sexual dysfunction and suicidal ideation in young men treated with low-dose finasteride: a pharmacovigilance study. *Pharmacotherapy* 2015;35(7):687-95.
5. Irwig MS. Depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects. *J Clin Psychiatry* 2012;73(9):1220-3.
6. Irwig MS. Safety concerns regarding 5α reductase inhibitors for the treatment of androgenetic alopecia. *Curr Opin Endocrinol Diabetes Obes* 2015;22(3):248-53.
7. Traish AM, Hassani J, Guay AT, 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;8(3):872–84.

8. Ganzer CA, Jacobs AR, Iqbal F. Persistent sexual, emotional, and cognitive impairment post-finasteride: a survey of men reporting symptoms. *Am J Mens Health* 2015;9(3):222-8.
9. Caruso D, Abbiati F, Giatti S, et al. Patients treated for male pattern hair with finasteride show, after discontinuation of the drug, altered levels of neuroactive steroids in cerebrospinal fluid and plasma. *J Steroid Biochem Mol Biol* 2015:146:74-9.
10. *Adverse events of 5-alpha-reductase inhibitors*. Bethesda (MD): National Institutes of Health, Office of Rare Diseases Research, Genetic and Rare Diseases Information Center; updated 2015 Mar 3. (accessed 2015 Sept 10)
11. *Proscar, Propecia (finasteride)* [prescribing information]. Whitehouse Station (NJ): Merck Sharp & Dohme Corp., Inc.; 2013, 2014. (accessed 2015 Sept 28)
12. *Proscar, Propecia (finasteride)* [summary of product characteristics]. Hoddesdon (UK): Merck Sharp & Dohme Limited; 2013, 2015. (accessed 2015 Sept 28)

HELPFUL LINKS

- MedEffect™ Canada
- Recalls and Safety Alerts Database
- Summary Safety Reviews
- New Safety Reviews
- Canada Vigilance Adverse Reaction Online Database
- Drug Product Database
- Medical Devices Active Licence Listing
- Licensed Natural Health Products Database
- The Drug and Health Product Register
- Canadian Drug Shortage Database

Suggestions?

Your comments are important to us. Let us know what you think by reaching us at InfoWatch_InfoVigilance@hc-sc.gc.ca

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Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

Due to time constraints relating to the production of this publication, information published may not reflect the most current information.

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