Summary Safety Review - Testosterone Replacement Products - Cardiovascular Risk

July 15, 2014

Issue

A safety review was initiated to evaluate the currently available information regarding the possible cardiovascular risk (heart and blood vessel problems) associated with the use of testosterone replacement products. In the course of its normal activities, Health Canada observed a growing body of evidence suggesting a possible association between the use of testosterone replacement products and cardiovascular risk. This evidence, and in particular a scientific article published in November 2013\(^1\), prompted this detailed assessment.

Background

Approved use of testosterone replacement products in Canada

In Canada, there are 12 testosterone-containing products that are currently marketed for use as testosterone replacement therapy: ANDRIOL, ANDRODERM, ANDROGEL, AXIRON, DELATESTRYL, DEPO-TESTOSTERONE, TESTIM and their equivalent generics. These products are approved for use in adult males who are experiencing medical conditions because their body cannot make enough testosterone. Testosterone replacement products should not be used in men for non-specific symptoms if laboratory tests have not been done to confirm a low testosterone level, and if other possible causes of symptoms have not been excluded.

Cardiovascular risk

Cardiovascular risk refers to the risk of a group of heart and blood vessel problems that can include, but is not limited to, heart attacks, strokes, blood clots in the lungs or legs, and an irregular heart rate. It is known that testosterone replacement therapy may cause an increase in blood pressure and fluid retention/swelling. In addition to these risks, testosterone replacement products may also cause blood vessel narrowing by promoting the build-up of fats and other materials in the inner walls of blood vessels. This narrowing of blood vessels makes it harder for blood to flow through, and if a blood clot forms and blocks the flow of blood, it may cause a heart attack or stroke. Testosterone replacement products may also cause blood clots in the lungs or legs by affecting blood clotting processes.

At the time of this review, the Canadian product label for testosterone replacement products identified the risk of high blood pressure, as well as fluid retention/swelling (particularly in persons with underlying heart problems).

Objective

To assess the available evidence concerning the cardiovascular risk, beyond the known risks of high blood pressure and fluid retention/swelling, which may be linked to testosterone replacement products. This review considered information from Canadian adverse reaction reports, scientific literature, international safety data, as well as what is known about the use of these products both in Canada and internationally. The review evaluated the risk and suggested ways to minimize it.
Key Findings

Use of testosterone replacement products in Canada

Similar to the trend in other countries, prescriptions for testosterone replacement products in Canada have been increasing. Testosterone was most commonly prescribed to men aged 40-59 years. The elderly population (65 years old and over) is the second most prescribed age group.

Canadian reports of cardiovascular problems in Canada associated with the use of testosterone replacement products

As of Aug. 31, 2013, Health Canada received 35 reports of cardiovascular problems involving testosterone replacement products. Some of these reports described the problem as disappearing after the patient stopped using the product or as re-appearing when the patient re-started the product after having temporarily stopped it. This may support a possible link between cardiovascular risk and testosterone replacement products. Some of the reports also described patients with current, or a history of, conditions (e.g., diabetes and high blood pressure) that may also be associated with the reported cardiovascular problems. In 11 of the 35 reports, heart attack, blood clots in the lungs, or irregular heart rate were considered possibly related to testosterone therapy.

Scientific reports

Several studies conducted after marketing suggest an increased risk of serious cardiovascular problems (e.g., heart attack and stroke) that may be linked to testosterone replacement products. Although these studies have limitations, they provide evidence in support of this possible association when considered as a whole.

Additional cases of cardiovascular problems, such as blood clots in the lungs and legs, have also been reported in the literature, as well as in other countries. Some of these cases also described the problem as disappearing after the patient stopped using the product or as re-appearing after the patient re-started the product after having temporarily stopped it.

Conclusions and Actions

The current available evidence suggests the possibility that cardiovascular problems, other than those already identified, may occur with the use of testosterone replacement products. The use of these products in Canada (and internationally) has been increasing and findings from a Canadian study raise additional concerns that these products may not always be used within the approved patient population.

Health Canada actions:

1. Health Canada is working with manufacturers to update the Canadian product label for testosterone replacement products regarding possible cardiovascular risks including heart attack, stroke, blood clots in the lungs or legs, and irregular heart rate;
2. Health Canada has communicated to Canadians on the possible cardiovascular risk associated with testosterone replacement products; and
3. Health Canada is collaborating with foreign regulators including the United States Food and Drug Administration and the European Medicines Agency regarding this safety concern.

Health Canada will keep Canadians informed and take action, as appropriate, if any new safety information is identified.

Full Review Reports

Full review reports are available upon request to Marketed Health Products Directorate. These


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2. IMS utilization data provided by: IMS Health Canada Inc. An external party cannot refer to nor use IMS data, which have been generated by Health Canada, without a Third Party Agreement in place.
3. This list of references is not intended to be exhaustive. References have been selected as suggestions for further reading and reflect the most current information at the time of the safety review.

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