Health Canada Santé Canada

June 4, 2014

Notice

Our file number: 14-105859-93

Prescription Drug List (PDL): Lovastatin

The purpose of this Notice of Intent to Amend is to notify that, as a result of consultation, Health Canada will revise the listing for lovastatin on the Prescription Drug List (PDL). Only the Human part of the PDL is to be revised; the listing for Veterinary use will remain unchanged. In 2009 Health Canada conducted a scientific review of lovastatin against a set of established and publicly available criteria for prescription status (see http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/schf_annf_fact_pol-eng.php). These factors are consistent with the new criteria outlined in section C.01.040.3 of the *Food and Drug Regulations* that define a prescription drug. Public consultation was communicated in a Notice of Intent published in the *Canada Gazette*, Part I, December 26, 2009. As a result of this consultation the wording is:

Drugs containing any of the following:	Lovastatin *Lovastatine*
Including (but not limited to)	
Qualifier	except in oral dosage form that provides 1 milligram (mg) or less per daily dose *sauf sous forme posologique orale à une concentration de 1 milligramme (mg) ou moins par dose quotidienne.*
Effective Date	six months from the date of this Notice

Consultation summary:

Comments were received from six respondents: two associations of manufacturers of health products; an association of health care practitioners; and three companies associated with the manufacturing and marketing of health products. One respondent expressed support for the revision. The other five respondents had concerns about the wording for the revised listing for lovastatin. The issues and concerns raised by the five respondents are summarized below with Health Canada's responses.

Canada

Comment (1)

The proposed regulatory amendment must prevent the ability of manufacturers to add lovastatin up to the 1.0 mg limit in natural health products.

Health Canada's Response (1)

The amendment to the current listing of Lovastatin on the PDL would require all oral dosage form products to comply with the limit of 1 mg or less per daily dose. This limit would be applicable to both products with naturally occurring and/or synthetically added Lovastatin.

Comment (2)

A normal Asian diet of red yeast rice would exceed the proposed 1.0 mg amount of lovastatin therefore the 10% should be applied to a lower therapeutic limit of 20 mg to allow exemption from prescription status for oral dosage forms containing 2.0 mg per dose or per daily dose.

Health Canada's Response (2)

The United States Food and Drug Administration (FDA) analyzed 33 samples of red yeast rice (RYR) and RYR food products to compare levels of lovastatin in traditional foods with levels of lovastatin in dietary supplements. The FDA found that 30 of the RYR foods contained no lovastatin whatsoever, two contained approximately 0.012% lovastatin, and one contained approximately 0.066% lovastatin, all far lower concentrations than those of dietary supplements. Health Canada accepts the FDA's conclusion that RYR traditional foods do not contain significant amounts of lovastatin. That evidence helps to explain the safety of the traditional foods. Health Canada does not support increasing the prescription threshold to 2.0 mg per dosage unit or per daily dose.

Comment (3)

Red yeast rice traditional Chinese or Japanese medicines will be at risk of not being allowed in Canada unless they are modified to reduce the monacolin K[1] content. However, if the content is reduced they will not be approved by the Natural Health Products Directorate (NHPD) as the method of preparation will not fit that of the Pharmacopoeia (Chinese)[2].

Health Canada's Response (3)

Red yeast rice fermented according to traditional methods that results in a finished product providing less than 1.0 mg per dosage unit or per daily dose is consistent with the Chinese and Japanese literature on traditional medicinal uses of RYR and would be potentially eligible for licensing as a traditional medicine

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1 Red yeast rice is the product of yeast grown on rice, and it contains several compounds collectively known as monacolins, substances known to inhibit cholesterol synthesis. One of these, "monacolin K," is also known as mevinolin or lovastatin.

2 Pharmacopoeia is a book issued by an officially recognized authority to serve as a standard for describing drugs, chemicals, and medicinal preparations. Examples include the British Pharmacopoeia (BP), Chinese Pharmacopoeia (ChP), United States Pharmacopoeia (USP).

natural health product in Canada. However, it is important to note that the Chinese Pharmacopoeia contains not only traditional medicines but some modern pharmacological agents and preparations. Thus, a RYR product with a pharmacopoeial method of preparation that results in high lovastatin content, that is (i.e.) containing 1.0 mg or more of lovastatin will be regulated as a prescription drug in Canada.

Comment (4)

Hypercholesterolemia is not a Schedule A disease state and therefore no regulatory restrictions are encountered with cholesterol reduction claims. The necessity of physician supervision for the treatment of high cholesterol is not justified in this case as other products have already been approved by the NHPD for the same purpose.

Health Canada's Response (4)

Schedule A to the *Food and Drugs Act* (Act) is a list of diseases, disorders or abnormal physical states for which section 3 of the Act prohibits advertising to the general public and labelling of foods, drugs, cosmetics and devices as a treatment or cure. Prevention and risk reduction claims for these conditions are permitted for natural health products, as per sections 103.2 and 103.3 to the *Natural Health Products Regulations*. Schedule A is not an exhaustive list of diseases, disorders or conditions for which therapeutic products may require a prescription. The factors for listing a drug as prescription do not refer to specific diseases, disorders or conditions but to various risk factors, such as the need for direct practitioner supervision for individualized instructions and monitoring, particularly for vulnerable patients, and the presence of known adverse side effects at normal therapeutic doses. For these reasons many drugs used to treat hypercholesterolemia, including lovastatin at greater then 1.0 mg per dosage unit or per day, and any dose of atorvastatin, cerivastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin remain available by prescription only. Alternatively, some products indicated for the prevention or risk reduction of high cholesterol and for the maintenance of healthy cholesterol levels have been authorized as non-prescription natural health products.

Comment (5)

Red yeast rice preparations have been found by a number of researchers to possess other active compounds that may have additive action with monacolin K to produce the observed cholesterol lowering effects. It is important to note that lovastatin as a therapeutic drug is an isolate, whereas red yeast rice extract is not. It is our opinion (i.e., an industry stakeholder group) that lovastatin (monacolin K) found in red yeast rice should be exempt from any dose limitation as this will significantly impact the access for all Canadians to this traditional and scientific-based ingredient intended to be used at therapeutic dosages. The Stakeholder does not support this proposal as written and asks that the dose restriction be removed based upon available safety and efficacy data.

Health Canada Response (5)

Health Canada has reviewed all available evidence for the safety of lovastatin and concluded that the factors for prescription status at doses greater than 1.0 mg per dosage unit or per day still apply. There is insufficient evidence to support the position that at any given dose above this threshold, the pharmacology and toxicology of lovastatin as a component of an extract of RYR would be so different from its pharmacology and toxicology as an isolated pure substance that the broad principles for determining prescription status would not apply. Recognizing the research showing other active constituents in red

yeast rice, this amendment enables market authorization under the *Natural Health Products Regulations* for RYR products that naturally contain no more than a trace amount of lovastatin and may provide health benefits due to these other constituents. The *Natural Health Products Regulations* and the *Food and Drug Regulations* also provide a regulatory framework for clinical trials that could further investigate the potential for an additive interaction between RYR health products and lovastatin to lower cholesterol levels in a safe and effective manner.

Comment (6)

Red yeast rice providing lovastatin will only be able to be used in multi ingredient products at sub-therapeutic dosages, which will be a disadvantage to Canadians seeking natural health product alternatives in combating high cholesterol. Products containing less than 1.0 mg daily of lovastatin will be unable to support any cholesterol lowering claims as this level is sub-therapeutic.

Health Canada's Response (6)

It is well established that some health products (for example, made from an extract of red yeast rice) contain a pharmacologically relevant, bioavailable dose of lovastatin. Any health product providing lovastatin at a dose greater than 1.0 mg daily will remain subject to the prescription requirements of the *Food and Drug Regulations* since, due to the safety issues referred to above, and consistent with other international jurisdictions, health care practitioner oversight and monitoring of lovastatin use is important particularly in vulnerable patients where there may also be risk of potential drug-drug/natural health product/food interactions. This amendment allows RYR health products with no more than a trace amount of lovastatin but with other beneficial natural constituents, alone or as a component of multi-ingredient natural health products, to be marketed in order to provide Canadians with alternatives that help maintain health and reduce the risks of high cholesterol and associated health problems. Health Canada has determined that these purposes are appropriate for nonprescription health products.

Result of Consultation:

Based on this consultation Health Canada intends to revise the listing for lovastatin non-prescription use. The revision above will be in effect six months from the date of this Notice through a Notice of Amendment posted on the Health Canada website.

Should you have any questions on this update to the Prescription Drug List, please contact:

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