Health Canada Santé Canada

Graham Spry Building
250 Lanark Avenue
A.L. 2005D
Ottawa ON K1A 0K9

05-125671-845

Provincial and Territorial Deputy Ministers of Health
Provincial and Territorial Drug Program Managers
Deans of Pharmacy
Registrars of Provincial Medical and Pharmacy Associations
Industry and Consumer Associations
Regulatory and Health Professional Associations
Other Interested Parties

Dear Sir/Madam:

Re: *Food and Drug Regulations* - Project # 1490 - Schedule F

This letter is to provide an opportunity for comment on the proposed addition of a medicinal ingredient to Part I of Schedule F to the *Food and Drug Regulations*.

Schedule F is a list of medicinal ingredients, the sale of which is controlled under sections C.01.041 to C.01.049 of the *Food and Drug Regulations*. Part I of Schedule F lists ingredients that require a prescription for human use and for veterinary use. Part II of Schedule F lists ingredients that require a prescription for human use, but do not require a prescription for veterinary use if so labelled or if in a form unsuitable for human use.

The Drug Schedule Status Committee determines the necessity for prescription status for medicinal ingredients on the basis of established and publicly available criteria. These criteria include, but are not limited to, concerns related to toxicity, pharmacological properties and therapeutic uses of the ingredients.

.../2

Description of the medicinal ingredient:

Tramadol and its salts is a centrally acting synthetic opioid (narcotic) analgesic that is indicated for the short-term (five days or less) management of pain. Although its mode of action is not completely understood at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. It is not recommended for minor pain that may be treated adequately through lesser means where benefit does not outweigh the possible opioid-related side effects. Tramadol and its salts is contraindicated in any situation where opioids are contraindicated, including acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs.

The degree of regulatory control afforded by Schedule F (prescription drug) status coincides with the risk factors associated with this medicinal ingredient. Oversight by a practitioner is necessary to ensure that adequate risk/benefit information is available before the drug containing the medicinal ingredient is administered and that the drug therapy is properly monitored.

Alternatives

Consideration was given to recommending that tramadol be listed on a schedule to the Controlled Drugs and Substances Act (CDSA). The CDSA limits the possession, importation, exportation, production, distribution and sale of narcotics, controlled drugs, targeted substances and precursor chemicals that can result in harm when distributed or used without controls. The CDSA specifies restrictions and offences that apply to drugs that are subject to abuse and illicit activity. These more stringent limits to access help to prevent the diversion of these substances for illegal purposes. The CDSA includes six schedules that list controlled substances and precursor chemicals, each associated with different offences, penalties and controls. The CDSA is a tool used to implement Canada's obligations under the United Nations drug control conventions.

Tramadol is not listed in any of the Schedules to the United Nations drug control conventions; therefore, Canada is not obligated to control it under the CDSA. In September 2002, the World Health Organization (WHO) Expert Committee on Drug Dependence conducted a critical review to determine if tramadol should be added to the Schedules of the United Nations drug control conventions. The WHO found that the information available was not sufficient to recommend international control; however, it was recommended that tramadol be kept under surveillance.

.../3

Tramadol is marketed as a prescription drug in 87 countries. Seventeen countries have extra controls in place; however, this does not include any of the larger developed countries such as the US, Germany, Australia, UK, and Switzerland. Tramadol has been on the market in Germany since 1977 and in the US since 1995. Tramadol is not regulated as a controlled substance in either country; there have been no changes in scheduling status based on experience with this drug in these two countries since it was first introduced there. The international scheduling profile for tramadol does not support a recommendation that tramadol be scheduled as a controlled substance in Canada.

Tramadol hydrochloride is synthesised from salicylic acid through numerous reactions. It cannot be considered to belong to any family or group listed in the Schedules to the CDSA, nor chemically related to any substance currently listed in the CDSA. There is insufficient evidence to support a recommendation to schedule tramadol under the CDSA at this time.

A risk management strategy to support the safe and effective use of tramadol and its salts under Schedule F has been established. The following are considered to be the essential components of the risk management strategy:

a) Commitment to not emphasize or highlight the scheduling status of tramadol and its salts in its advertising or promotional activities.

b) Inclusion of an approved fair balance statement in all tramadol and its salts advertising and promotional materials.

c) Provision of progress reports to Health Canada from the ongoing drug abuse surveillance program, including data from four key informant Canadian sites in the program.

d) Reassessment of the success of the risk management strategy 2 years post product launch.

Benefits and Costs

The amendment would impact on the following sectors:

- **Public**

Prescription access to drug products containing this medicinal ingredient would benefit Canadians by decreasing the opportunities for improper use and by ensuring the guidance and care of a practitioner.

Another benefit is that drug products for human use containing medicinal ingredients listed on Schedule F may be covered by both provincial and private health care plans.

.../4

- **Health Insurance Plans**

Drug products for human use containing medicinal ingredients listed on Schedule F may be a cost covered by both provincial and private health care plans.

- **Provincial Health Care Services**

The provinces may incur costs to cover practitioners' fees for services. However, the guidance and care provided by the practitioners would reduce the need for health care services that may result from improper use of drug products for human use that contain medicinal ingredients listed on Schedule F. The overall additional costs for health care services should therefore be minimal.

Compliance and Enforcement

This amendment would not alter existing compliance mechanisms under the provisions of the *Food and Drugs Act* and the *Food and Drug Regulations* enforced by the Health Products and Food Branch Inspectorate.

Consultation

The manufacturer affected by this proposed amendment was made aware of the intent to recommend this medicinal ingredient for inclusion on Schedule F during the review of the drug submission.

The process for this consultation with stakeholders is described in the Memorandum of Understanding (MOU) to streamline regulatory amendments to Schedule F, which came into effect on February 22, 2005. The MOU is posted on the Health Canada website.

This letter is being sent by email to stakeholders and is also being posted on the Health Canada website and the Consulting Canadians website.

Any comments regarding this proposed amendment should be addressed as follows within **75** days following the date of posting of this letter on the Health Canada website. The policy analyst for this project, Ginette Chalifoux, may be contacted at:

Project No. 1490
Policy Division
Policy Bureau
Therapeutic Products Directorate
1600 Scott Street, Holland Cross
Tower 'B', 2nd Floor
A.L. 3102C5
Ottawa, Ontario K1A 0K9
telephone: 613-948-4623 (refer to Project No. 1490)
facsimile: 613-941-6458 (refer to Project No. 1490)
email: regaff_access@hc-sc.gc.ca

.../5

Final Approval

In accordance with the MOU process, it is anticipated that this amendment will proceed directly from this consultation to consideration for final approval by the Governor in Council, approximately 6 to 8 months from the date of posting of this letter on the Health Canada website. If approved by the Governor in Council, publication in the *Canada Gazette*, Part II, would follow. The amendment would come into force on the date of registration.

Yours sincerely,

Original signed by

Neil Yeates
Acting Assistant Deputy Minister