Canada Gazette
Welcome to the official newspaper of the Government of Canada published since 1841

Vol. 141, No. 27 — July 7, 2007

Order Amending Schedule I to the Controlled Drugs and Substances Act

Statutory authority

Controlled Drugs and Substances Act

Sponsoring department

Department of Health

REGULATORY IMPACT ANALYSIS STATEMENT

(*This statement is not part of the Order.*)

Description

The purpose of this initiative is to add the substance tramadol to Schedule I to the *Controlled Drugs and Substances Act* (CDSA) and to the Schedule to the *Narcotic Control Regulations* (NCR).

Tramadol is a centrally acting synthetic analgesic and an opioid agonist of the morphine type. It is currently being sold in Canada in two formulations: as a low-dose combination product containing 37.5 mg of tramadol and 325 mg of acetaminophen, and as a single entity extended release formulation containing between 150 mg and 400 mg of tramadol.

When the first formulation of tramadol was approved for sale in 2005, tramadol was not scheduled under the CDSA or the NCR because it was to be marketed as a combination low-dose product and was not considered to pose a significant risk in terms of abuse or dependence. Tramadol was therefore recommended for inclusion in Schedule F to the *Food and Drug Regulations* (FDR), and the drug product was approved on the condition that the sponsor carry out post-market monitoring for drug abuse liability and

dependence. Schedule F to the FDR is a list of medicinal ingredients that, when contained in a drug product, require that the product can only be sold or dispensed pursuant to a prescription issued by a practitioner.

The submission of an application for a second formulation of tramadol as a single entity extended release product triggered another review of this substance and whether or not it should be scheduled under the CDSA and its regulations.

Scheduling

The CDSA provides a legislative framework that prohibits and penalizes illicit activities with controlled substances unless otherwise authorized by regulations for medical, industrial or scientific purposes. Substances regulated under the CDSA can alter mental processes and may produce harm to the health of an individual or to society when diverted or misused. The substances controlled under the CDSA are grouped into six schedules, and each schedule is associated with specific offences and punishments described in Part I of the Act.

The NCR regulates the activities of producers, distributors, importers, exporters, health care professionals, and hospitals as they pertain to narcotic drugs. The NCR does not prevent practitioners from prescribing a substance when it is required for the medical condition for which their patient is being treated. Advertising to the general public is not possible under the NCR.

In determining if and in which schedule a substance should be regulated under the CDSA and its related regulations, Health Canada considers several factors including international requirements and trends, the dependence potential and likelihood of abuse or misuse of the substance, the extent of its abuse or misuse in Canada, the danger it represents to the safety of the public, and the usefulness of the substance as a therapeutic agent.

International requirements and trends in control/scheduling

Tramadol is not listed under the United Nations Single Convention on Narcotic Drugs 1961 or the Convention on Psychotropic Substances 1971; therefore, Canada is not obligated to control it under the CDSA.

Tramadol is marketed as a prescription drug in 75 countries, and a few others are considering adding extra controls or are monitoring the substance closely. For instance, in 2005 the US Food and Drug Administration and the US Drug Enforcement Administration (DEA) received several petitions from the public appealing for tighter control on tramadol under the *Controlled Substances Act* (CSA). Those petitions urged the US federal government to include tramadol in the CSA as a Schedule III substance due to it being an opioid analgesic with abuse liability and dependence potential. At the present time, tramadol continues to be listed on the *List of Drugs and Substances of Concern* published by the DEA.

In addition, 29 countries currently have extra controls in place for products containing tramadol (e.g. Italy, Austria, Taiwan, Brazil and the United Arab Emirates).

Dependence potential and likelihood of abuse/misuse

The magnitude of the risk of abuse and dependence potential associated with tramadol has not been definitively characterized in Canada.

Notwithstanding, at doses ranging from 50 mg to 2 000 mg (see footnote 1) per dose, clinical and non-clinical studies have shown that tramadol and its main metabolite can cause dependence in a manner comparable to some other opioid analgesics such as oxycodone or morphine.

Product monographs for extended release formulations of tramadol state that it can be abused in a manner similar to other opioid agonists. In particular, extended release formulations could be abused by dissolving, crushing, chewing, or snorting the product, which may result in uncontrolled delivery of the opioid, and could result in overdose and death.

Extent of abuse/misuse in Canada

As mentioned previously, tramadol products have been on the market in Canada since 2005, and are available to patients with a valid prescription from a medical practitioner. Prescription drugs that are not scheduled under the CDSA and its regulations are not subject to importation, exportation, production, distribution, manufacturing data reporting requirements or loss and theft reporting requirements; therefore, information regarding the extent of misuse and abuse of tramadol is lacking. This is not unexpected given that if the low-dose combination product (37.5 mg of tramadol and 325 mg of acetaminophen) were to be consumed in amounts producing the desired opioid effect, it could result in liver toxicity or other ill effects due to the large amount of acetaminophen ingested.

Finally, a recent study (see footnote 2) published in the *Canadian Medical Association Journal* has revealed that drug abusers are turning to prescription opioids such as oxycodone, codeine, and morphine, rather than heroin at an increasing rate. Therefore, it is reasonable to foresee that higher dose formulations of tramadol may be abused or misused in the future.

Danger to public health and safety

Non-clinical studies have shown that high doses of tramadol can cause drug dependence and fully substitute for other opioid analgesics such as morphine. Thus, the risk of tramadol being abused and consequently causing physical and/or psychological harms is increased.

The single entity tramadol formulations recently approved or currently under review by Health Canada contain up to 400 mg of tramadol per dose. Higher dose formulations will provide a sufficient amount of the substance for drug abusers to obtain an opioid effect if misused.

Since tramadol was first marketed in Canada in 2005, Health Canada has received 58 adverse drug reaction reports associated with tramadol use. Although the amount of tramadol in the product cited in the adverse drug reaction reports is considerably low, 30 cases reported reactions similar to those that can be commonly caused by opioid

analgesics.

Control of tramadol under the CDSA and NCR will minimize the health risks associated with its illicit use. It will serve to minimize its diversion due to the increased security requirements while still allowing practitioners, when required, to prescribe tramadol to their patients.

Legitimate use in Canada

Tramadol has been on the market as an analgesic in a number of different countries since 1977. It has a long history of use as an analgesic and there is no question of its legitimate therapeutic application.

While Schedule F to the FDR ensures some level of control over distribution, the potential for diversion, particularly with extended release formulations of tramadol, may not be sufficiently mitigated without the additional controls required by scheduling under the CDSA and the NCR. These additional controls, which include enhanced reporting and record keeping, affect activities at both manufacturing sites and sites involved in the distribution chain such as pharmacies, medical clinics, and hospitals.

Alternatives

Health Canada considered three options during the scheduling analysis of tramadol, which are as follows:

Option 1: Proceed to add tramadol to Schedule F to the FDR

It was determined that the placement of tramadol solely under the FDR would not adequately address the risks associated with the abuse liability and dependence potential of the substance; therefore, the potential risks for abuse and/or misuse would not be mitigated. In addition, Schedule F to the FDR does not provide adequate controls to prevent the possible diversion of tramadol to illicit channels.

Option 2: Add tramadol to Schedule III or IV to the CDSA

Schedules I, II and III are subject to the same offences with varying punishments. These offences include possession, trafficking, possession for the purpose of trafficking, importation, exportation, possession for the purpose of exportation, and production. The offences for Schedule IV are similar to those of Schedules I, II, and III, except that there is no offence for simple possession.

Substances in the schedules to the CDSA tend to be grouped together according to their pharmacological properties. Tramadol shares many pharmacological properties with substances found under Schedule I to the CDSA, which consists of other opioid analgesics such as morphine. Schedules III and IV to the CDSA generally consist of substances such as amphetamines and anabolic steroids respectively.

Risks caused by the abuse and/or misuse of tramadol are not comparable to those of other substances in Schedules III and IV; therefore, these options were not pursued.

Option 3: Add tramadol to Schedule I to the CDSA and the Schedule to the NCR

Addition of tramadol under Schedule I to the CDSA and the Schedule to the NCR is selected as the best option as it will minimize the risk of tramadol diversion. Tramadol is similar to the substances already in this schedule (e.g., morphine, codeine, and oxycodone), and penalties and offences would be consistent with other opioid analgesics. Proactive measures, such as increased control on manufacturing, distribution, import, and export will reduce the risk of tramadol products being abused or misused.

Controlling tramadol under the CDSA and the NCR will also address the concerns raised by medical professionals and professional associations, such as the National Association of Pharmacy Regulatory Authorities (NAPRA) regarding the potential for misuse and/or abuse. This option will ensure that practitioners and pharmacists are aware of the abuse potential of tramadol when prescribing, dispensing, or storing it in order to prevent non medical and illicit use and diversion of the substance. The controls under the CDSA and NCR will also prevent advertising of tramadol products to the general public.

Benefits and costs

The increased control over the distribution of tramadol will affect practitioners, pharmacists, hospitals, the pharmaceutical industry, law enforcement, and the Canadian public.

Practitioners, pharmacists, and hospitals

Practitioners, pharmacists and hospitals who administer or provide tramadol to patients will now be required to meet the requirements of the NCR which include

- Written, signed and dated orders or prescriptions only;
- Increased record-keeping requirements;
- Increased security measures; and
- Reporting of loss or theft.

The impact on these groups is expected to be minimal as most practitioners, pharmacists and hospitals already use or distribute drugs regulated under the NCR and have the required security measures in place, as well as experience with the various record-keeping requirements.

Pharmaceutical industry

Persons that fabricate, package or label, perform tests, distribute, import or wholesale products containing Schedule F drugs require an establishment licence to carry out these functions as prescribed by section C.01A.008 of the FDR. In order to perform these functions in relation to products containing tramadol, importers, exporters, manufacturers and distributors would also have to obtain a licence under the NCR and/or have their existing dealer's licence amended to include tramadol. It will also be necessary to obtain import and export permits for each transborder shipment of tramadol.

Licensed dealers will be required to keep more detailed records concerning acquisitions

and disbursements of all tramadol products and to report thefts and losses to Health Canada.

All of the companies who manufacture tramadol products on the market in Canada and/or the products that are currently under review already hold licences for dealing in controlled substances under the Regulations to the CDSA.

Manufacturers will also be required to change their product labels as all drugs regulated under the NCR must display an "N" on the outside labels as dictated by section C.01.004 of the FDR. The incremental costs associated with the change in regulatory status of tramadol is expected to be minimal for these manufacturers, and reasonable transition periods will be established to minimize the cost associated with these labelling changes.

Law enforcement

Placement of tramadol under Schedule I to the CDSA will allow for certain offences to be charged against persons conducting illegal activities with tramadol. It will also enable law enforcement officers to take action against persons who are not authorized to import, export, produce and/or possess tramadol. Law enforcement agencies and prosecutors may incur additional costs in dealing with offences under the CDSA in relation to tramadol; however, these actions should ultimately serve to decrease the illicit activity in respect of this substance and are not significantly high in comparison to other opioid analgesics.

Canadian public

This regulatory amendment will benefit Canadians as the increased control of tramadol will serve to minimize its diversion, and the health risks associated with its illicit use. At the same time however, this amendment will not affect the availability or use of tramadol for legitimate medical or scientific purposes.

It is clear that the benefits outweigh the costs associated with scheduling tramadol under the CDSA and regulating it under the NCR.

Consultation

The following groups were consulted with during the development of this proposal:

- Drug Enforcement Administration, US Department of Justice;
- Bureau of Cardiology, Allergy and Neurological Sciences, Therapeutic Products Directorate, HPFB, Health Canada;
- Marketed Pharmaceuticals and Medical Devices Bureau, Marketed Health Products Directorate, HPFB, Health Canada;
- Drug Branch, Royal Canadian Mounted Police;
- Drug Analysis Services, Drug Strategy and Controlled Substances Programme (DSCS), Healthy Environments and Consumer Safety Branch (HECS), Health Canada; and
- Office of Research and Surveillance, DSCS/HECS, Health Canada.

Stakeholders were informed of the proposed scheduling of tramadol by a Letter to

Stakeholders issued in March 2007. The proposal is supported by other stakeholders including health professional associations like NAPRA, and provincial and territorial licensing bodies such as the College of Pharmacists of British Columbia, and the Saskatchewan College of Pharmacists. Many of these groups have stated that other opioid analgesics are controlled under the CDSA and it would be inconsistent not to regulate tramadol in a similar manner.

Two manufacturers of tramadol have voiced concerns regarding the proposal to schedule tramadol under the CDSA. Health Canada has met with both companies and explained its rationale for scheduling tramadol under the CDSA.

Compliance and enforcement

Enforcement activities are carried out by local and federal law enforcement agencies. This amendment will provide law enforcement with the tools necessary to combat illegal possession, trafficking, importation, exportation, and production of tramadol. Offences under the CDSA are subject to criminal prosecution. Monitoring of compliance with the NCR is the responsibility of Health Canada. This amendment will not alter existing compliance mechanisms. Failure to comply with the Regulations could lead to administrative sanctions, such as revocation of a licence or permit, or criminal prosecutions.

Contact

Shereen Khan
Office of Controlled Substances
Drug Strategy and Controlled Substances Programme
Healthy Environments and Consumer Safety Branch
Address Locator: 3503D
Ottawa, Ontario
K1A 1B9
Telephone: 613-946-0121
Fax: 613-946-4224
Email: OCS_Policy_and_Regulatory_Affairs@hc-sc.gc.ca

PROPOSED REGULATORY TEXT

Notice is hereby given that the Governor in Council, pursuant to section 60 of the *Controlled Drugs and Substances Act* (see footnote a), deeming that it is necessary in the public interest, proposes to make the annexed *Order Amending Schedule I to the Controlled Drugs and Substances Act*.

Interested persons may make representations concerning the proposed Order within 75 days after the date of publication of this notice. All such representations must cite the *Canada Gazette*, Part I, and the date of publication of this notice, and be addressed to Shereen Khan, Office of Controlled Substances, Drug Strategy and Controlled Substances Programme, Healthy Environments and Consumer Safety Branch, Department of Health, MacDonald Building, Address Locator: 3503D, 123 Slater Street, Ottawa, Ontario K1A 1B9 (fax: 613-946-4224; e-mail: OCS_Policy_and_Regulatory_Affairs@hc-sc.gc.ca).

Ottawa, June 21, 2007

MARY O'NEILL
Assistant Clerk of the Privy Council

ORDER AMENDING SCHEDULE I TO THE CONTROLLED DRUGS AND SUBSTANCES ACT

AMENDMENT

1. Schedule I to the *Controlled Drugs and Substances Act* (see footnote 3) is amended by adding the following after item 18:

19. Tramadol ((1R,2R)-rel-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol) and its salts

COMING INTO FORCE

2. This Order comes into force on the day on which it is registered.

[27-1-o]

Footnote 1

Swedish Medical Products Agency, *Withdrawal Reactions from Tramadol - A Bigger Problem than Expected?*, Internet document: Four pages, November 14, 2006, www.lakemedelsverket.se.

Footnote 2

Fischer, B., Rehm, J., Patra, J., Firestone Cruz, M. (2006). "Changes in illicit opioid use across Canada". *Canadian Medical Association Journal*, 175(11), 1385-1387.

Footnote a

S.C. 1996, c. 19

Footnote 3

S.C. 1996, c. 19

NOTICE:
The format of the electronic version of this issue of the *Canada Gazette* was modified in order to be compatible with hypertext language (HTML). Its content is very similar except for the footnotes, the symbols and the tables.

Top of page

Maintained by the Canada Gazette Directorate
Updated: 2007-07-06

Important notices