# Canada Gazette, Part 1, Volume 153, Number 16: Regulations Amending the Narcotic Control Regulations (Tramadol)

April 20, 2019

**Statutory authority**
*Controlled Drugs and Substances Act*

**Sponsoring department**
Department of Health

## REGULATORY IMPACT ANALYSIS STATEMENT

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

### Issues

Tramadol is a synthetic opioid analgesic that has been marketed in Canada since 2005. It is regulated under the *Food and Drugs Act* (FDA), and is available by prescription only. Like other opioid analgesics, while tramadol can provide effective pain relief for some patients, it has potential for problematic use, and chronic use of tramadol can lead to tolerance and dependence. Tramadol can also cause harmful adverse effects that pose risks to human health, which can be fatal in some cases. Tramadol is suspected to have contributed to 18 reported deaths in Canada between 2006 and 2017.

The crisis of overdoses and deaths caused by opioids is of national concern in Canada. Canada is the world's second-largest consumer of prescription opioids per capita, and there have been increasing concerns related to access to prescription opioids due to their potential for diversion and problematic use, both within Canada and globally. While problematic use of tramadol has not contributed significantly to the opioid crisis in Canada, it is a significant and growing public health concern in other countries, and it represents a potential threat to the health and safety of Canadians.

Unlike most opioid analgesics, tramadol is not controlled under the *Controlled Drugs and Substances Act* (CDSA) or regulated under the *Narcotic Control Regulations* (NCR). Controlling tramadol would strengthen Health Canada's (HC or the Department) oversight of legitimate activities with tramadol, and facilitate detection and prevention of diversion. It would also enable Canadian law enforcement agencies to take enforcement action against a broader range of unauthorized activities with tramadol, such as the seizure of unauthorized shipments of tramadol. This would help to mitigate the risk of problematic tramadol use emerging as a significant threat to the health and safety of Canadians.

### Background

#### *Pharmacology*

Opioids are a class of drugs that have analgesic properties, and the proper use of prescription opioids can be helpful for managing pain for some patients. However, opioids can also produce effects, such as euphoria, that create the potential for problematic use. Opioids can also cause harmful adverse effects, including potentially fatal respiratory depression, and can produce tolerance and dependence with chronic use.

By itself, tramadol is a weak opioid. When ingested, tramadol is partly broken down into the more potent opioids, *O*-desmethyltramadol (M1) and *N*,*O*-didesmethyltramadol (M5). Most of tramadol's opioid-related effects are attributable to M1, with tramadol itself contributing to some extent. M5 is not produced in sufficient quantity to contribute significantly to the aforementioned effects; however, if it was produced outside the body in sufficient quantities, it could be converted to M1 through a simple chemical process.

Unlike most opioids, tramadol also has properties of a serotonin and norepinephrine reuptake inhibitor (SNRI). These properties contribute to tramadol's analgesic effect, but can also cause harmful adverse events such as seizures and serotonin syndrome, which can be fatal in some cases. The likelihood of these events increases with dosage, or if tramadol is taken in combination with other drugs that affect serotonin.

The potency of tramadol's SNRI- and opioid-related effects depends on how much of the drug is converted to M1 before it reaches the brain. This can vary significantly due to genetic factors, and some individuals will experience much more potent (or much weaker) opioid effects from the same dose of tramadol compared to the average patient. It is not feasible to identify those individuals prior to initiating treatment, which can have implications for patient safety.

#### *Medical use*

Tramadol is used primarily as an analgesic. While it is considered to be a weak opioid, it can be administered in dosages that provide pain relief comparable to low therapeutic doses of more potent opioid analgesics, but cannot be safely taken in higher doses due to the risk of SNRI-related adverse effects.

Tramadol is available in Canada by prescription only, and is authorized for human and veterinary use. It is indicated for the treatment of moderate to moderately severe pain, but is also known to be prescribed "off-label" as a treatment for other conditions, most commonly for ejaculation dysfunction. Tramadol was one of six opioids that accounted for over 96% of opioid prescriptions in Canada between 2012 and 2016.

#### *Regulatory framework*

The CDSA is the means by which Canada fulfills its obligations under the United Nations Single Convention on Narcotic Drugs, 1961; the United Nations Convention on Psychotropic Substances, 1971; and the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988. These conventions form the basis for the current global drug control system. The CDSA provides for the control of substances that can alter mental processes, and that may produce harm to health and to society when diverted or misused, and of chemical precursors that can be used to synthesize these substances.

The CDSA prohibits certain activities with the substances listed in its schedules, unless they are authorized by the CDSA regulations, or through an exemption pursuant to subsection 56(1) of the Act. The CDSA also specifies the range of penalties associated with the conduct of illegal activities with controlled substances and chemical precursors.

The CDSA regulations define the conditions for conducting authorized activities with the controlled substances listed in their schedules. Opioid analgesics are generally scheduled under the NCR and are subject to the corresponding requirements. For example, dealers licensed to produce, distribute, import and export substances scheduled under the NCR must comply with requirements for secure handling and storage, record keeping, and reporting of loss and theft of those substances. Further requirements for secure storage of controlled substances at licensed dealer sites are outlined in HC's *Directive on Physical Security Requirements for Controlled Substances* (Security Directive). Non-compliance with these requirements may result in the suspension or revocation of a licence or permit, or a referral for criminal prosecution.

This framework protects public health and maintains public safety by balancing the need for access to these substances for legitimate medical, scientific, and industrial purposes, and the need to minimize the risk of diversion to illegal markets and uses.

#### *Scheduling history*

In 2007, HC published a Notice of Intent in the *Canada Gazette*, Part I, indicating the Department's intent to add tramadol to Schedule I to the CDSA and to the schedule to the NCR.

While health professional associations and provincial and territorial licensing bodies were generally supportive of the proposed amendments, most of the feedback provided by other stakeholders raised concerns that scheduling was not warranted.

HC subsequently commissioned external reviews of tramadol's chemistry and pharmacology, which were completed in 2008. After considering the review findings and the data available at the time, the Department did not proceed to control tramadol.

#### *Current status*

There is now more evidence that high doses of tramadol could have potential for problematic use comparable to some opioids controlled under Schedule I to the CDSA, such as meperidine (marketed as Demerol®). Between 2006 and 2017, tramadol is suspected to have contributed to 71 adverse events related to problematic use, dependence or withdrawal reported in Canada, and to over 7 000 reported internationally. Problematic tramadol use is also reported to be a serious and growing public health concern for many countries, particularly in Africa and Western Asia.

There have also been nine reported deaths in Sweden linked to use of "herbal krypton," a preparation that included M1. These reports found no evidence for the presence of tramadol, which implies that the M1 may have been produced for direct consumption.

Although the available evidence does not suggest that M5 has significant potential for problematic use, it does present a risk due to the fact that it can be converted into M1.

### Objective

By placing legislative controls on tramadol, M1 and M5, the proposed amendments would serve to help mitigate the health and safety risks of problematic use of these substances. Such amendments would provide law enforcement with the power to take action against any unauthorized activities with these substances while allowing HC to regulate legitimate activities with these substances, including their use for medical and other legitimate purposes. The proposed amendments would also complement existing initiatives implemented

under the Canadian Drugs and Substances Strategy, which aims to balance public health and public safety objectives through the four pillars of prevention, treatment, harm reduction, and enforcement.

## Description

***Order Amending Schedule I to the CDSA***

This Order would amend Schedule I to the CDSA to include tramadol, M1 and M5, as well as the salts, isomers, and salts of isomers of tramadol, M1 and M5.

***Regulations Amending the Schedule to the NCR***

The proposed Regulations would amend the Schedule to the NCR to include tramadol, M1 and M5, as well as the salts, isomers, and salts of isomers of tramadol, M1 and M5.

## Regulatory development

***Consultations***

On June 16, 2018, HC published a notice to interested parties (NTIP) in the *Canada Gazette*, Part I, indicating the Department's intent to add tramadol to Schedule I to the CDSA and to the Schedule to the NCR. The Department received feedback from 20 respondents, most of whom expressed support for the proposed amendments.

**Health care professionals, organizations, and regulatory bodies**

Feedback from health care professionals and related organizations was generally supportive. Many of these stakeholders stated that tramadol can produce euphoria and dependence similar to other opioids, and that it should be regulated in the same way as those substances.

Some stakeholders also suggested that controlling tramadol could help dispel misperceptions about its safety for medical use compared to other prescription opioids. Some also noted that tramadol could pose additional risks for some populations because of its variable potency.

**Industry**

Stakeholders from industry advised that scheduling tramadol would create regulatory burdens for firms that supply tramadol products, such as additional import time required to obtain import permits. They also noted that some firms would need to make changes to their infrastructure to store inventories of tramadol in compliance with the physical security requirements for substances regulated under the NCR.

While none of these stakeholders objected to controlling tramadol under the CDSA, some noted that firms that did not work with substances regulated under the NCR might choose to discontinue their activities with tramadol rather than comply with the new requirements. One also suggested that the physical security measures required for products regulated under the NCR were not necessary to prevent diversion of tramadol, while others emphasized the importance of allowing firms sufficient time to implement the required changes to avoid disruptions in supply.

Based on the input received and further discussions with industry, HC is proposing that the amendments take effect 365 days after their final publication in the *Canada Gazette*, Part II.

**Wildlife rehabilitation**

One organization involved in wildlife rehabilitation indicated that they use tramadol to provide analgesia for sick and injured animals. Most wildlife rehabilitators are not licensed veterinarians, and they rely on veterinarians to provide them with prescription drugs to administer to the animals in their care following protocols established by the veterinarian. The organization believes that if tramadol was controlled, their veterinarian would no longer be able to prescribe tramadol to have on hand in case of an emergency (e.g. to treat an injured animal hit by a car). The organization expressed concern that some wildlife rehabilitators would not be able to provide adequate analgesia to the animals in their care if they did not have access to an easy-to-administer, non-controlled opioid analgesic such as tramadol.

Veterinarians prescribe drugs to individual animal patients in a similar manner that doctors do for their human patients. However, when there are large numbers of animal patients (e.g. a herd of cattle that may require treatment), veterinarians may also prescribe for the entire herd. This is how drugs are often prescribed to wildlife rehabilitators to treat the animals in their care. Non-controlled alternatives to tramadol available to wildlife rehabilitators include analgesics such as non-steroidal anti-inflammatory drugs (e.g. meloxicam, carprofen); alpha-2 adrenergic receptor agonists (e.g. medetomidine); local anesthetics (e.g. lidocaine). These alternative drugs may have additional safety concerns and often require additional skills to administer safely in comparison to tramadol.

Veterinary use of controlled pharmaceutical drugs is regulated at the federal, provincial and territorial levels. HC consulted provincial and territorial veterinary licensing authorities to determine if any existing regulations or practice guidelines could prevent veterinarians from providing wildlife rehabilitators with controlled drugs. Five provincial licensing bodies responded, but only one identified a potential barrier to this practice in their jurisdiction. The potential barrier stems from a professional practice regulation that prohibits veterinarians from dispensing controlled drugs and narcotics to treat free-ranging wildlife. The animal must be under the direct care of the veterinarian to be treated with controlled drugs. The provincial veterinary licensing authority indicted that it was working with veterinarians to determine an acceptable path forward, should tramadol become controlled under the CDSA. The veterinary licensing authorities that responded to the consultation request indicated support for the scheduling of tramadol.

**Patients**

Some respondents raised concerns that controlling tramadol could create barriers to access for patients. One respondent that supported controlling tramadol also stressed the importance of hearing patient concerns, and of ensuring that access to appropriate pain management is not compromised. Some respondents that did not support the proposal provided anecdotes about tramadol's therapeutic value, or questioned the evidence of tramadol's actual or potential for problematic use.

HC has reviewed the evidence of tramadol's potential for problematic use and has found that it may be comparable to some controlled opioids, which is supported by reports of problematic use from other jurisdictions (e.g. Africa, Asia).

Tramadol is already identified as a prescription drug on HC's Prescription Drug List (PDL). If tramadol was controlled under the CDSA and NCR, patients would continue to obtain tramadol from a practitioner or by a written prescription, but verbal prescriptions would no longer be permitted for tramadol products currently marketed in Canada. This is not expected to have a significant impact on patient access.

Over the last year, HC has consulted with clinicians and researchers involved in the treatment of chronic pain and pain management, as well as patients living with chronic pain. The Department recognizes that some patients who suffer from chronic pain have experienced increased stigma as a result of the attitudes and beliefs around the use of opioids in the context of the current opioid crisis. The Department has also heard from patients living with chronic pain who have encountered inconsistencies in treatment services. HC is committed to working with Canadians living with pain, and clinicians and researchers to increase knowledge and implementation of best practices in pain management and to improve the health of Canadians experiencing pain.

***Modern treaty obligations and Indigenous engagement and consultations***

An assessment of modern treaty implications found that the proposed Regulations are not expected to have an impact on Canada's modern treaty obligations.

Indigenous organizations and self-governing bodies were notified when the NTIP for this proposal was posted in the *Canada Gazette*, Part I. None of the feedback received during the comment period identified concerns specific to Indigenous populations.

***Instrument choice***

The proposed amendments would help protect Canadians from the health and safety risks associated with the unauthorized use of tramadol. If tramadol is not controlled under the CDSA, it will continue to be available by prescription only, and subject to federal, provincial and territorial regulations for prescription drugs. These measures may not be as effective in facilitating the detection and prevention of unauthorized activities with tramadol, or preventing problematic tramadol use. Activities with M1, M5, and other substances related to tramadol would be largely unregulated.

Accordingly, controlling tramadol under the CDSA is recommended. The most effective instrument to achieve this purpose is through the proposed amendments because these changes would strengthen surveillance of tramadol prescribing practices, and provide Canadian law enforcement agencies with the authority to take action against unauthorized activities with tramadol and related substances.

## Regulatory analysis

***Benefits and costs***

A cost-benefit analysis was conducted to assess the impacts of the proposed amendments on potentially affected stakeholders (i.e. the pharmaceutical industry, patients, health practitioners, pharmacists, the Government of Canada, and provincial and territorial governments). All identified costs and benefits are assessed in incremental terms by considering changes that would only occur as a result of the proposal.

Identified impacts are quantified and monetized to the extent possible. Where this is not possible due to data limitations or a lack of sufficient information, the impacts are assessed qualitatively. Together, the quantified and non-quantified impacts provide a more complete picture of the costs and benefits to stakeholders and allow for an adequate assessment of the proposal's net impact.

All quantifiable costs and benefits were estimated over a period of 10 years, from 2019–2020 to 2028–2029. This time period is considered long enough for all the costs and benefits to manifest themselves sufficiently.

All costs and benefits are expressed in 2017 constant Canadian dollars. A 7% real discount rate is used to estimate the present value (PV) of the quantified and monetized impacts, and all values are discounted to the year 2019.

The proposed amendments would benefit Canadians as they would help mitigate the health and safety risks associated with the growing utilization (including problematic use) of tramadol and potentially lessen the associated socio-economic burden. However, the amendments will also increase administrative and compliance burdens for the pharmaceutical industry and other stakeholders. These costs and benefits are discussed below. Overall, the proposed amendments are expected to result in net benefits to Canadian society.

## Benefits

In Canada, the consumption of tramadol has been increasing over the past few years in contrast to that of other opioids; the volume of tramadol sales per capita rose from 126.9 mg in 2000 to 161.5 mg in 2017. Studies have shown that opioid-related harms due to problematic use are positively correlated with the utilization level of prescription opioids. It is then reasonable to assume that the continued growth in tramadol consumption could result in significant impacts on public health in the long-term.

Adding tramadol to Schedule I to the CDSA and the Schedule to the NCR is expected to result in changes to physicians' prescribing approach and patients' perception and attitudes toward the drug, contributing together to a reduction in the consumption of tramadol products, as it did in other jurisdictions that took a similar approach, like the United Kingdom (U.K.) It is assumed that, if tramadol is controlled, physicians would follow the same approach (e.g. meeting requirements under the NCR and re-evaluating a patient's health status before deciding to continue with prescribing tramadol) as when prescribing other controlled opioids. At the same time, the increased awareness of patients regarding tramadol's negative health effects, coupled with recent changes to the *Food and Drug Regulations* requiring opioid warning stickers and patient information handouts, could remove the potential misperception of the drug being safer, which would make them more cautious when using the drug. In addition, as per the NCR, verbal prescriptions and refills would not be permitted for tramadol products currently marketed in Canada, thereby ensuring patients always consult with their physicians before further tramadol can be prescribed.

It is expected that the proposals would contribute to reducing tramadol use, similar to patterns observed in the United Kingdom and some states in the United States following similar actions taken by these jurisdictions. In the United States, the states of Kentucky and Arkansas added tramadol to their list of controlled substances in 2008 and 2009, respectively. While consumption of tramadol continued to grow in other states that did not take similar actions, the use of tramadol in Kentucky and Arkansas decreased by 4% and 31%, respectively. At the federal level, there is no readily available information on potential reduction of tramadol use following listing of the substance by the United States in 2014.

Similarly to what was observed for the two U.S. states mentioned above, a study in the United Kingdom indicated a 13% drop in the monthly utilization of tramadol after the opioid was controlled in 2014. While it cannot be stated with a high degree of certainty that these actions were the only reasons for these total reductions, the statistics presented above suggest that the controls placed on tramadol contributed to a large degree to the reductions observed in these countries. Similarly to what was observed in those jurisdictions, the proposed amendments are expected to result in a decrease in the utilization of tramadol in Canada. This could translate into a reduction in the incidence of tramadol-related adverse events with associated reductions in morbidity and premature mortality cases.

### Reduction in morbidity cases and hospital visits

Between 2006 and 2017, there were 71 reported cases of adverse health events (e.g. gastrointestinal disorder, seizure, overdose, dependence or withdrawal) linked to tramadol use, including its problematic use. It is expected that the reduction in the use (including problematic use) of tramadol could lead to a reduction in the incidences of adverse health events and the need for medical intervention. This would potentially result in cost savings to the healthcare system. The cost savings would only be associated with the number of avoided tramadol-related harmful cases that would have led to interventions from health emergency services and hospital stays. However, there is no information at the national level that can be used to assess how significant the impact of the proposed amendments would be on preventing these adverse health events. As a consequence, this benefit has not been estimated but acknowledged qualitatively.

### Reduction in premature mortality

Between 2006 and 2017, there were 18 reported deaths potentially related to tramadol use. The available information on the reported cases does not distinguish between intended suicides and accidental deaths. However, the June 2018 "National Report: Apparent opioid-related deaths in Canada" indicated that 92% of the deaths associated with opioids were unintentional. It is therefore reasonable to assume that most of the 18 tramadol-related deaths were accidental. Subjecting tramadol to the same strict controls placed on other opioids under the CDSA would help prevent its problematic use and ultimately contribute to reducing the number of cases of premature mortality associated with the substance. The U.K. study found that the number of tramadol-related deaths per 100 000 inhabitants decreased from 0.42 in 2014 to 0.36 in 2015, a 14% decrease after the listing of tramadol in 2014. It is expected that overtime, a similar positive outcome would be observed in Canada.

### Other benefits

Controlling tramadol would help strengthen monitoring of activities related to tramadol, which would support evidence-based interventions to address any continued risks to Canadians. The proposed amendments would strengthen HC's oversight of legitimate activities with tramadol, and facilitate detection and prevention of diversion to illicit activities.

## Costs

### Costs to pharmaceutical industry

There are currently 19 Canadian pharmaceutical companies supplying 35 pharmaceutical drugs containing tramadol in the Canadian market. If the proposed amendments are made, to continue their activities (e.g. manufacturing, packaging or distributing) with tramadol, these companies would have to undertake the administrative and compliance activities described below and carry the associated incremental costs. In total, incremental costs to the pharmaceutical industry are expected to be $1.058 million over 10 years (or $150,656 annually).

#### *Administrative costs*

Among the 19 Canadian pharmaceutical companies, 5 are not licensed under the CDSA and thus, are not authorized to conduct activities with controlled substances. If the proposed amendments are implemented, these 5 companies would need to apply for dealer's licences in order to continue their activities with tramadol and would face the associated incremental administrative costs. It is assumed that the 5 companies operate a total of eight sites (or facilities) where activities with tramadol are conducted. Thus, they would need to apply for eight licences and incur incremental administrative costs related to

- applying for, amending (whenever necessary) and renewing their licences;
- applying for permits should they need to import or export tramadol;
- keeping records, and submitting monthly and annual reports;
- becoming familiar with the regulatory requirements; and
- reporting suspicious transactions.

The 14 companies that currently hold valid licences to conduct business with controlled substances would also carry incremental administrative costs to continue their activities with tramadol, but to a lesser extent in comparison to the 5 companies that do not hold licences. Based on available information and feedback from industry, it is estimated that these 14 companies operate 20 sites where activities are conducted with tramadol. These companies would bear a one-time administrative cost to amend their licences to include tramadol and would also carry ongoing administrative costs associated with applying for permits in order to import or export tramadol. In addition, the companies would have to spend additional time to report information on tramadol in their monthly and annual reports, as well as to report suspicious transactions.

With respect to import/export permits, it is assumed that about 60 permits each year would be required by affected companies.

Completing the activities mentioned above usually involves someone with a technical or scientific background such as a qualified person in charge (QPIC) or alternate QPIC (AQPIC) and someone at the management level such as a senior person in charge (SPIC). The hourly wages of a QPIC/AQPIC and SPIC used for this analysis are $30.40 and $62 (adjusted for overhead and in 2017 dollars), respectively. Table 1 presents the activities and time required for QPICs/AQPICs and SPICs to complete each of the administrative tasks.

Table 1: Administrative activities and associated time

| Administrative Tasks | Time (hours/year) | |
|---|---|---|
| | QPIC or AQPIC | SPIC |
| Applying for new licences[table 1 note *] (one-time) | 3 | 1 |

**Table 1 Notes**

Table 1 Note *

New licence holders only.

Return to table 1 note * referrer

Table 1 Note **

Administrative cost related to suspicious transactions is not estimated due to lack of information regarding incident cases.

Return to table 1 note ** referrer

| | | |
|---|---|---|
| Renewing existing licences[table 1 note *] (every three years) | 1 | 0.5 |
| Applying for a criminal record certificate[table 1 note *] (every three years) | 2 | 2 |
| Applying for import/export permits (as required) | 0.75 | 0.25 |
| Submitting annual reports: | | |
| • new licence holders<br>• existing licence holders | 2<br>1 | 0.5<br>0.5 |
| Submitting monthly reports: | | |
| • new licence holders<br>• existing licence holders | 18<br>6 | 3<br>3 |
| Reporting suspicious transactions[table 1 note **] | 0.17 | – |
| Reviewing and understanding the regulatory requirements[table 1 note *] (upfront) | 4 | 2 |

**Table 1 Notes**

Table 1 Note *

New licence holders only.

Return to table 1 note * referrer

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Administrative cost related to suspicious transactions is not estimated due to lack of information regarding incident cases.

Return to table 1 note ** referrer

The total incremental administrative costs to the pharmaceutical industry would be $185,690 (or $26,438 annually).

***Compliance costs***

Some of the sites that currently hold a valid dealer's licence deal with large volumes of tramadol products that are not necessarily stored in a secure area. If the proposed amendments are made, access to these products would need to be controlled and as a consequence, they would need to be stored in an area that meets physical security requirements and is approved by HC under the NCR and the Security Directive. It is expected that the current physical security installations at these sites are not large enough to accommodate the volume of tramadol products and would need to be expanded. Based on readily available information on the size of the tramadol business of these companies, it is expected that about three licensed sites would need to make changes to their security installations and would carry the associated incremental compliance costs. The average cost to modify the security areas at these sites is assumed to be the same as the cost that would be assumed to build a new secure area, as indicated below.

The five companies whose sites would need to become licensed dealers would also need to have on-site secure storage areas and apparatus to store controlled substances in order to meet the requirements of the Security Directive. In addition to the administrative costs, each of the eight sites owned by the five companies would need to spend about $70,000 on average in upfront capital costs, to establish the storage area. They would also need to spend about $1,000 each year to maintain the security environment for each licensed site.

Each of the eight sites would also carry costs to obtain and renew licences. These costs would consist of fees paid to acquire criminal record certificates for all QPIC/AQPICs and SPIC (five individuals on average per site, $60 per individual) and a $5,082 licensing fee paid upon renewal.

The total incremental compliance costs to licensed dealers would be $872,452 (or $124,218 annually).

***Impact on revenues and profits***

The expected reduction in the level of tramadol use may have a negative impact on tramadol sales revenues and potentially the profits of businesses. Evidence from the United Kingdom and the United States indicates that tramadol sales decreased after the substance was scheduled by these jurisdictions. In the United States, tramadol sales revenue decreased at a faster pace once tramadol was classified as a schedule IV substance under the *Controlled Substances Act*. While a decrease could be expected for Canadian businesses as well, there is uncertainty as to the likelihood and magnitude of such a decrease. In addition, given the mix of products being offered and potential therapeutic product substitution, the reduction in sales for one product might be compensated by an increase in sales of another, making the potential impact on company profits uncertain, but qualitatively acknowledged.

**Costs to patients**

Patients may be impacted by the proposed amendments, depending on their particular circumstance. Some patients already have to see their doctor each time they need to get a renewal of their prescription, while others received a prescription that includes a specific number of refills. Since verbal prescriptions and refills of tramadol products currently marketed in Canada would no longer be allowed, patients who would have otherwise obtained a prescription verbally or with refills would need to see their doctor to be reassessed so a decision can be made with respect to whether the patient should continue with the medication and receive a prescription.

Patients could therefore be faced with the inconvenience of having to go to and wait for a doctor to get their prescription renewed. There might be cases where some patients would face delays in accessing their medication as they are waiting for an appointment. However, the likelihood of this happening is considered to be very low given that patients could be proactive and seek an appointment well in advance of running out of their medication. While these impacts are acknowledged, it is not possible to assess them quantitatively because information on the number of patients and the frequency of visits to get a prescription renewed is not readily available.

**Costs to health practitioners**

Should tramadol become a controlled substance, health practitioners who are authorized to prescribe would be required to report losses and thefts of tramadol within 10 days of an incident; however, using tapentadol, a similar opioid that is a controlled substance, for which there has been no report of loss or theft during the last year, as proxy, it is anticipated that there would be a low risk of loss and theft incidents related to tramadol in health practitioners' clinics.

**Costs to pharmacies**

As is the case for practitioners, pharmacies would also be required to report losses and thefts within 10 days of an incident. Currently, losses and thefts of tramadol (if any) are unknown given that there is no obligation to report these incidents for non-controlled substances to the federal government. However, using tapentadol, a similar opioid that is a controlled substance, as a proxy, it is anticipated that approximately 20 cases of loss and theft incidents per year related to tramadol may be reported by pharmacies in Canada. It is assumed that a pharmacist would spend approximately an hour per incident to complete a loss and theft report.

In addition, pharmacies would face incremental administrative costs in terms of keeping records and documenting information on tramadol to meet federal and provincial requirements with respect to the distribution of narcotic drugs. There are currently 10 947 licensed pharmacies in Canada that could be affected by the proposed amendments. It is assumed that a pharmacist would spend approximately an hour per year to complete this activity.

Using an hourly wage of $47.71 (adjusted for overhead and in 2017 dollars) for a pharmacist, the total incremental costs to pharmacies to report losses and thefts and to keep records on activities related to tramadol would be $3.186 million (or $453,636 annually).

**Costs to the federal government**

The Government of Canada would incur limited incremental costs related to processing permit applications, which are not recovered through fees. Based on the number of permits expected to be received by HC over the analytical period, it is estimated that the total incremental cost to the Government of Canada in processing applications would be $12,750 in PV over 10 years (or $1,815 annually).

HC would also devote effort to process applications for new licences and the renewal of site licences, as well as amendments to licences to include tramadol. The level of effort by the Department to process these applications is fully cost recovered through the receipt of licensing fees. There is therefore no incremental cost to the Government of Canada associated with this activity.

To support the implementation of the proposed amendments, limited compliance promotion activities such as publishing web materials to continue to raise awareness about the proposed requirements, contacting targeted stakeholders and responding to enquiries would be undertaken. These activities would be conducted in the first year of implementation and would result only in negligible incremental costs to the Department. Similarly, enforcement activities are not expected to be significant. Based on applications submitted to HC, a pre-licence inspection would take place (when the site is ready) to ensure that sites that are currently not licensed dealers are in compliance with the Security Directive. The Department would incur an upfront cost of $750 to conduct these inspections. The licensed dealers would then fall within the Department's risk-based approach for inspections, which would be conducted as part of normal operations, and no resources would be specifically assigned to conduct tramadol-related inspections. Overall, the incremental effort associated with compliance promotion and enforcement activities will be very limited, since these types of activities fall within normal compliance activities, and there will be no change in the manner in which the NCR is currently enforced.

#### Costs to provincial and territorial governments

Provincial and territorial health care programs might be impacted as these programs would need to cover the costs associated with additional doctor visits in order for patients to get their prescriptions renewed. Due to limitations of available information, it is not possible to provide a quantitative assessment of these impacts.

### Net impacts

The proposed amendments subject tramadol to the same regulatory controls as other opioid analgesics. These proposed modifications are expected to contribute to the protection of public health and public safety, stemming from the potential changes in both prescribing practices by practitioners and users' perception and attitude towards the drug, potentially leading to a reduction in the utilization of tramadol. Reduced utilization of tramadol would contribute to reduced incidences of adverse health outcomes associated with tramadol use, including problematic use. While these potential benefits are considered significant, it was not possible to provide quantitative estimates due to the lack of reliable and appropriate data.

The proposed amendments would also impose costs on affected stakeholders. Industry would face incremental administrative and compliance costs in order to continue its activities with tramadol. Patients, practitioners, pharmacists, federal, provincial and territorial governments would also carry costs but most of these costs are considered minimal and are discussed qualitatively. The quantified and monetized costs to stakeholders amount to $4.3 million over 10 years or $606,191 on an annualized basis (see Table 2). Overall, taking into account both quantified and non-quantified impacts and considering the potential health and safety benefits, it is expected that the proposal would result in a net benefit to Canadian society.

Table 2: Cost-benefit analysis summary

| A. Quantified Impacts (2017 $) | 2019–2020 | 2028–2029 | Total (10 years) | Total (PV) | Annualized Value |
|---|---|---|---|---|---|
| | | Undiscounted | | Discounted to the Year 2019 | |
| | | **A1. Costs to pharmaceutical industry** | | | |
| | | **Administrative costs** | | | |
| Applying for a licence | $1,227 | $0 | $1,227 | $1,147 | $163 |
| Acquisition of a criminal record certificate | $2,941 | $2,941 | $11,765 | $8,319 | $1,184 |
| Renewing a licence | $0 | $492 | $1,475 | $931 | $133 |
| Amending licences | $1,229 | $0 | $1,229 | $1,149 | $164 |
| Submitting annual and monthly reports | $15,213 | $15,213 | $152,135 | $106,853 | $15,213 |
| Keeping records | $0 | $8,000 | $72,000 | $48,712 | $6,935 |
| Applying for import/export permits | $0 | $2,301 | $20,706 | $14,009 | $1,994 |
| Reviewing and understanding the amendments | $4,890 | $0 | $4,890 | $4,570 | $651 |
| **Total administrative costs** | **$25,501** | **$28,947** | **$265,426** | **$185,690** | **$26,438** |
| | | **Compliance costs** | | | |
| Licensing fees (payment of fees) | $0 | $40,656 | $121,968 | $77,002 | $10,963 |
| Criminal record certificate fees | $2,400 | $2,400 | $9,600 | $6,789 | $967 |
| Physical security | $772,200 | $11,000 | $871,200 | $788,661 | $112,288 |
| **Total compliance costs** | **$774,600** | **$54,056** | **$1,002,768** | **$872,452** | **$124,218** |
| **Total costs to industry** | **$800,101** | **$83,003** | **$1,268,194** | **$1,058,142** | **$150,656** |
| | | **A2. Costs to pharmacists** | | | |
| | | **Administrative costs** | | | |
| Filling in the transaction reports | $0 | $522,309 | $4,700,779 | $3,180,339 | $452,809 |
| Submitting loss and theft reports | $0 | $954 | $8,588 | $5,810 | $827 |
| Total administrative costs to pharmacists | **$0** | **$523,263** | **$4,709,367** | **$3,186,149** | **$453,636** |
| | | **A3. Costs to the federal government** | | | |
| Processing import/export permits | $0 | $1,173 | $10,557 | $7,142 | $1,017 |
| Conducting initial inspections | $6,000 | $0 | $6,000 | $5,607 | $798 |
| **Total costs to the federal government** | **$6,000** | **$1,173** | **$16,557** | **$12,750** | **$1,815** |
| **Total costs** | **$806,101** | **$607,439** | **$5,994,118** | **$4,257,041** | **$606,107** |
| | | **B. Non-quantified impacts** | | | |
| | | **B1. Benefits** | | | |
| Reduction in mortality and morbidity | A reduction in the number of mortality and morbidity cases are expected due to a reduction in the utilization of tramadol. This could translate in cost savings to health care services in Canadian jurisdictions. | | | | |
| | | **B2. Costs** | | | |
| Potential delays faced by patients | Patients would see an increased burden associated with having to see a physician every time a prescription needs to be renewed. | | | | |
| Reporting by pharmacists | Pharmacies would face an administrative burden related to reporting of loss or theft of tramadol as per regulatory requirements. | | | | |
| Federal government implementation cost | Incremental effort associated with compliance promotion and enforcement activities would be limited and would be conducted as part of normal compliance activities undertaken by the Department. | | | | |
| Provincial and territorial costs for health services | Provincial and territorial jurisdictions would also carry costs, as they would have to cover the cost for services associated with additional doctor visits. | | | | |

#### *One-for-one rule*

Given that the proposed amendments would result in incremental administrative burden to pharmaceutical companies and pharmacies conducting activities with tramadol, the one-for-one rule would apply, and the proposed amendments would be considered an "IN" under the one-for-one rule.

#### Administrative costs to impacted pharmaceutical companies

All 19 companies, for a total of 28 sites, would see an increase in administrative burden in order to meet the regulatory requirements as a result of tramadol being listed as a narcotic. The administrative costs would be more significant for 5 of the companies given that the sites they operate (a total of 8 sites) are not currently licensed dealers.

In order to continue their activities with tramadol, these 8 sites would now be required to

- apply for a licence and renew that licence every three years;
- acquire a criminal record certificate and include it in their licence application and licence renewal packages;
- apply for permits to conduct import and export transactions;
- keep records of activities related to tramadol for two years and submit monthly and annual reports on these activities to HC; and
- report any suspicious transactions.

In addition, the persons in charge at these facilities would also need to spend time reviewing and understanding the NCR to ensure compliance with the regulatory requirements.

The remaining 20 sites that are already licensed dealers would have to

- amend their existing licences to include tramadol as a controlled substance with which they are involved;
- apply for permits to conduct tramadol-related import and export transactions;
- spend additional time including tramadol information in their monthly and annual reports; and
- report suspicious transactions.

As mentioned earlier, completing the activities mentioned above usually involves a QPIC or AQPIC and an SPIC. The level of effort expressed in terms of time spent by QPICs and SPICs completing each of the above administrative tasks were estimated based on responses to a questionnaire received from licensed dealers in March 2018 and reported in Table 1. The time spent on these activities is valued using average wage rates of $28.40 and $57.90 per hour (adjusted for overhead and in 2012 dollars) for QPICs and SPICs, respectively.

#### Administrative costs to pharmacies

In order to continue their business with tramadol, all pharmacies would now be required to keep records of transactions involving tramadol and report any loss or theft of the drug.

Completing the activities mentioned above usually involves a pharmacist. The time spent (see Table 1 in the "Regulatory analysis" section) on these activities is valued using an average wage rate of $44.50 per hour (adjusted for overhead and in 2012 dollars).

#### Total administrative costs

As per the requirements of the *Red Tape Reduction Act* and the *Red Tape Reduction Regulations* (RTR), the administrative burden costs on all affected industry stakeholders are estimated using the prescribed formula in the RTR over a 10-year period (2019–2020 to 2028–2029) and discounted to the year 2012 using a 7% real discount rate. The total incremental administrative burden cost to all affected businesses (pharmaceutical companies and pharmacies) is estimated to be $1,953,293. The annualized incremental cost to

affected businesses is estimated to be about $278,105 or $25.40 per business. However, it should be noted that the cost per business is different depending on whether the business is a pharmacy or a pharmaceutical manufacturer. The annualized incremental cost to pharmaceutical companies is estimated to be $14,476 or $762 per company. For pharmacies, the annualized incremental cost is estimated to be $263,629 or $24.10 per pharmacy.

***Small business lens***

Although none of the 19 pharmaceutical companies identified as conducting business with tramadol are small businesses, most pharmacies in Canada are small businesses; therefore, the small business lens applies. However, the proposed amendments are not expected to result in significant costs for small businesses given that the cost per pharmacy is very small and estimated at $24.10 per year. Absorbing this cost is not expected to have a significant impact on their businesses.

Scheduling tramadol would subject this substance to all the requirements set out in the NCR, including requiring pharmacists to keep records of transactions and reporting any losses and thefts within 10 days of an incident. These activities are essential to the effective administration of the NCR and the additional information would assist the Department in taking appropriate measures to deter potential diversion of tramadol and in turn help protect the safety of Canadians. In light of the relatively low cost imposed on pharmacies, a flexible option was not considered necessary.

***Regulatory cooperation and alignment***

Tramadol is not controlled internationally. The World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) considered the findings from a critical review of tramadol at its meeting in November 2018, to inform a decision on whether to recommend tramadol for international control under the 1961 or 1971 conventions. The ECDD noted that as an opioid analgesic not subject to international control, tramadol is widely used in many countries where access to other opioids for the management of pain is limited. Although the review found that problematic use was occurring in many jurisdictions, the ECDD announced at the reconvened 61st session of the Commission on Narcotic Drugs meeting in early December 2018 that it would not recommend tramadol for international control.

While the ECDD was strongly of the view that the extent of abuse and evidence of public health risks associated with tramadol warranted consideration of scheduling, it did not recommend tramadol for international control at that time so that access to this medication would not be adversely impacted, especially in countries or crisis situations where there may be limited or no access to other opioid analgesics.

While international access to medicine in developing countries is an important consideration by the WHO when determining whether a drug should be internationally controlled, this access concern does not apply in Canada as it has a robust regulatory system that allows predictable medical access to controlled substances by prescription. HC's proposal that tramadol be added to the CDSA and the NCR has been made in consideration of global and national data, such as increasing prescription rates, growing numbers of adverse events and the potential risk to the health and safety of Canadians and the opioid crisis.

While there is no international obligation to control tramadol, it is regulated as a controlled substance in some jurisdictions, including the United States (Schedule IV to the *Controlled Substances Act*) and the U.K. (class C, Schedule II to the *Misuse of Drugs Act* 1971). Controlling tramadol under the CDSA would align Canadian actions with those jurisdictions.

***Strategic environmental assessment***

In accordance with the *Cabinet Directive on the Environmental Assessment of Policy, Plan and Program Proposals*, a preliminary scan found no evidence of potential for impact on the environment. Therefore, a strategic environmental assessment is not required.

***Gender-based analysis plus***

No gender-based analysis plus (GBA+) impacts have been identified for this proposal.

A preliminary sex and gender-based assessment was conducted as part of the regulatory development for the proposed amendments to determine whether they would affect a particular socio-economic group differently than others when compared to the status quo. Comparing the sex and gender differences in the use of tramadol and resulting adverse outcomes, the analysis tries to identify the possibility and evidence that women and men would be affected differently, leading to unequal distribution of benefits or costs from the amendments among genders.

To date, no scientific study has found a gender difference in the movement of tramadol into, though, and out of the human body, and the opioid-related health risks (e.g. respiratory depression, dependence, and addiction) are similar between men and women. Thus, physiologically, tramadol does not generate any differences among genders. However, the route of access to and use patterns of tramadol vary between the two genders:

- Women are more likely than men to be prescribed opioids, including tramadol, and are more likely to initiate opioid use through a physician, while men are more likely to obtain prescription opioids for free from friends and are more likely than women to purchase opioids from a drug dealer. Available data on both public and private drug plans indicates that more than half of the prescriptions were prescribed to females. The Ontario Drug Policy Research Network's report also indicates that women were more likely to be treated with an opioid for pain or coughs compared to men, while men were more likely to be dispensed an opioid to treat addiction compared to women.
- Men and women differ in the risk factors associated with the problematic use of prescription opioids. Men are significantly more likely than women to alter the route of administration by inhaling and injecting prescription opioids. Women are more likely to engage in problematic use of prescription opioids because of affective distress and men tend to misuse opioids because of legal and problematic behavioural issues.
- In addition, the distribution of all the incidences of adverse reactions to tramadol documented in the Canada Vigilance database is uneven among genders: 46.4% were female and 37.8% were male.

The assessment of GBA+ implications of the implementation of the proposed amendments did not uncover any potential for either gender to be affected differently than the other compared to their status quo. The patterns indicated above would persist after implementation and there would be no incremental changes in the differences observed among genders if tramadol was controlled under the CDSA.

In summary, there exist gender differences in the use of tramadol under the status quo. However, there is no evidence suggesting that the existing gender differences would be altered as a result of the proposed amendments. Thus, no GBA+ impacts have been identified for this proposal.

### Implementation, compliance and enforcement, and service standards

***Implementation***

The Order and the Regulations would come into force 365 days after their publication in the *Canada Gazette*, Part II. This would provide industry stakeholders time to implement any changes required to comply with the new regulatory requirements. During this time, HC would remove tramadol from the PDL, which does not include ingredients listed in CDSA schedules.

HC will notify stakeholders of the amendments upon publication. Additional information will be provided on the Government of Canada website.

***Compliance and enforcement***

HC is responsible for issuing licences, permits, and exemptions that authorize activities with controlled substances, and for monitoring compliance with the CDSA regulations and the conditions of exemptions. The Canada Border Services Agency supports compliance monitoring for controlled substances at the border.

Non-compliance may result in administrative sanctions by HC, such as the suspension or revocation of a licence or permit, or a referral for criminal prosecution. Federal, provincial and local law enforcement agencies are responsible for taking enforcement action in response to contraventions of the CDSA that are subject to criminal prosecution. Prosecution of these contraventions is the responsibility of the justice system.

Penalties for contraventions of the CDSA are defined in the Act, and vary by schedule. For offences committed with a Schedule I substance, the maximum penalty ranges from a $1,000 fine and six months of imprisonment for a first offence of simple possession, to life imprisonment for most other offences if they are prosecuted by indictment. For some indictable offences, a mandatory minimum penalty of one to three years of imprisonment may apply if certain conditions are met.

Provincial and territorial authorities are responsible for professional licensing for practitioners and pharmacists, who are authorized under the CDSA and its regulations to conduct certain activities with controlled substances. These authorities are also responsible for monitoring compliance with any provincial or territorial regulations or practice guidelines regarding controlled substances in their jurisdictions. Non-compliance may result in administrative sanctions by the licensing body. Under certain conditions, the Minister of Health also has the authority to issue notices prohibiting licensed dealers and pharmacists from conducting activities with controlled substances.

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## PROPOSED REGULATORY TEXT

Notice is given that the Governor in Council, pursuant to subsection 55(1) of the *Controlled Drugs and Substances Act*, proposes to make the annexed *Regulations Amending the Narcotic Control Regulations (Tramadol)*.

Interested persons may make representations concerning the proposed Regulations within 60 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 the Office of Legislative and Regulatory Affairs, Controlled Substances Directorate, Healthy Environments and Consumer Safety Branch, Department of Health, Address Locator: 0302A, 150 Tunney's Pasture Driveway, Ottawa, Ontario K1A 0K9 (email: hc.csd.regulatory.policy-politique.reglementaire.dsc.sc@canada.ca).

Ottawa, April 11, 2019

Jurica Čapkun
Assistant Clerk of the Privy Council

## Regulations Amending the Narcotic Control Regulations (Tramadol)

### Amendment

**1 The schedule to the *Narcotic Control Regulations* is amended by adding the following after item 18.1:**

- 19 Tramadol (2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol), its salts, isomers and salts of isomers and the following derivatives of tramadol and the salts, isomers and salts of isomers of these derivatives:
  - (1) *O*-desmethyltramadol (3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-phenol)
  - (2) *N,O*-didesmethyltramadol (3-[1-hydroxy-2-[(methylamino)methyl]cyclohexyl]-phenol)

### Coming into Force

**2 These Regulations come into force on the first anniversary of the day on which they are published in the *Canada Gazette*, Part II.**

# Canada Gazette, Part 1, Volume 153, Number 16: Order Amending Schedule I to the Controlled Drugs and Substances Act (Tramadol)

April 20, 2019

**Statutory authority**
*Controlled Drugs and Substances Act*

**Sponsoring department**
Department of Health

## REGULATORY IMPACT ANALYSIS STATEMENT

For the Regulatory Impact Analysis Statement, see the ***Regulations Amending the Narcotic Control Regulations (Tramadol)***.

### PROPOSED REGULATORY TEXT

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

Interested persons may make representations concerning the proposed Order within 60 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 the Office of Legislative and Regulatory Affairs, Controlled Substances Directorate, Healthy Environments and Consumer Safety Branch, Department of Health, Address Locator: 0302A, 150 Tunney's Pasture Driveway, Ottawa, Ontario K1A 0K9 (email: hc.csd.regulatory.policy-politique.reglementaire.dsc.sc@canada.ca).

Ottawa, April 11, 2019

Jurica Čapkun
Assistant Clerk of the Privy Council

## Order Amending Schedule I to the Controlled Drugs and Substances Act (Tramadol)

### Amendment

**1 Schedule I to the *Controlled Drugs and Substances Act* is amended by adding the following after item 26:**

- 27 Tramadol (2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol), its salts, isomers and salts of isomers and the following derivatives of tramadol and the salts, isomers and salts of isomers of these derivatives:
  - (1) *O*-desmethyltramadol (3-[2[(dimethylamino)methyl]-1-hydroxycyclohexyl]-phenol)
  - (2) *N*,*O*-didesmethyltramadol (3-[1-hydroxy-2-[(methylamino)methyl]cyclohexyl]-phenol)

### Coming into Force

**2 This Order comes into force on the first anniversary of the day on which it is published in the *Canada Gazette*, Part II.**