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Vol. 138, No. 29 — July 17, 2004

## Regulations Amending the Food and Drug Regulations (1397 — Schedule F)

*Statutory authority*

*Food and Drugs Act*

*Sponsoring department*

Department of Health

### REGULATORY IMPACT ANALYSIS STATEMENT

#### *Description*

The Therapeutic Products Directorate (TPD) of Health Canada intends to update Schedule F to the *Food and Drug Regulations* of the *Food and Drugs Act* by adding seven medicinal ingredients to Part I of Schedule F.

Schedule F is a list of medicinal ingredients, the sale of which is controlled under sections C.01.041 to C.01.046 of the *Food and Drug Regulations*. Part I of Schedule F lists medicinal ingredients which require a prescription for both human and veterinary use. Part II of Schedule F lists medicinal ingredients which 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 review and introduction of new drugs on the Canadian market necessitate periodic revisions to Schedule F.

The Therapeutic Products Directorate's Drug Schedule Status



Subcommittee reviews the status of medicinal ingredients contained in drugs proposed for marketing. A decision regarding the necessity for prescription versus nonprescription status was made for each of the medicinal ingredients listed in this proposed amendment on the basis of established and publicly available criteria. These criteria include, but are not limited to, concerns relating to toxicity, pharmacologic properties, and therapeutic applications. Proposed revisions to current listings on Parts I and II of Schedule F are also based on decisions made by this Subcommittee.

#### New listings

It is proposed that the following seven medicinal ingredients be added to Part I of Schedule F:

1. Adefovir and its salts and its derivatives — a nucleotide analogue. Adefovir dipivoxil is used to treat chronic hepatitis B, a serious and potentially life-threatening viral illness which primarily attacks the liver. Routine lab monitoring and periodic liver biopsies are part of therapy. Specialized knowledge is required to treat hepatitis B and its many potential complications.
2. Almotriptan and its salts — a selective 5-hydroxytryptamine <sub>1B/1D</sub> (5-HT <sub>1B/1D</sub>) receptor agonist. Almotriptan malate is used for the acute treatment of migraine attacks with or without aura in adults. Activation of receptors in the cranial arteries is believed to result in constriction of the arteries and relief of migraine headache. The safe use of almotriptan requires that patients receive individualized instructions and assessments by a medical practitioner.
3. Cetrorelix and its salts — gonadotropin-releasing hormone (GnRH) antagonist. Cetrorelix acetate injection is used to help control the release of eggs from the ovaries of women undergoing assisted conception procedures such as in-vitro fertilization. It acts by inducing a rapid, reversible suppression of gonadotropin secretion and the prevention of premature luteinizing hormone surges in women undergoing controlled ovarian hyper-stimulation. Cetrorelix acetate injection should be prescribed by physicians who are experienced in fertility treatment. Although the product may be self-administered, it requires direct practitioner supervision and continuous laboratory monitoring.

4. Ketanserin and its salts — serotonin S2 receptor antagonist. Ketanserin is indicated for the treatment of wounds in horses on or below the tarsal or carpal joints and to prevent the formation of excessive granulation tissue at these wound sites. It may require surgical intervention before use. The use of ketanserin requires individualized instructions and direct practitioner supervision.

5. Phenylpropanolamine and its salts and its derivatives for veterinary use — a sympathomimetic amine consisting of the racemic mixture of *d*- and *l*-norephedrine. Phenylpropanolamine hydrochloride (PPA) is used in female dogs for the long-term treatment of urinary incontinence associated with sphincter mechanism incompetence. An adequate diagnosis requires veterinary medical expertise. Prescription status would minimize the risk for a diversion of this product to human use.

Until 2001, PPA was widely used in humans as a nasal decongestant in a large number of cough and cold, sinus and allergy medications. During the 1990s, a link between PPA and haemorrhagic stroke was suspected. This was based on cases reported to the United States FDA and many involved young women using PPA as an appetite suppressant, often as the first dose. PPA was not approved for use as an appetite suppressant or weight-loss product in Canada. However, an association was also found in women taking a first dose of cough and cold medications containing PPA. Men were also considered to be at risk. By late 2000, studies confirmed a link between PPA and haemorrhagic stroke. Given the risk of a serious event such as haemorrhagic stroke and the fact that medications containing PPA were used in Canada for relatively mild conditions and provided only temporary relief, Health Canada advised consumers not to use any products containing PPA until a full medical and scientific evaluation was completed. In 2001, Health Canada completed the evaluation and initiated a recall of all remaining PPA-containing products from the wholesale and retail market. Consumers were advised not to use any products containing PPA. All remaining products containing PPA were removed from the market.

The chemical structure of PPA is such that it has the potential to be used in the manufacture of illicit drugs. Since January 1, 2003, PPA has been listed on Schedule VI of the *Controlled Drugs and Substances Act* (CDSA) and is subject to the requirements of the *Precursor Control Regulations* (PCR). As

such, there is no requirement for a prescription but there are controls over import/export, production, distribution and sale. This scheduling under the CDSA and PCR does not prevent PPA from being placed on Schedule F of the *Food and Drug Regulations* as well. Schedule VI relates to precursor chemicals and it is recognized that these chemicals have a variety of uses that are not medically related. For this reason, it has been deemed acceptable to have a substance on CDSA VI to control its potential use in the manufacture of illicit drugs and at the same time, on Schedule F to control its use as a pharmaceutical agent. Having dual scheduling adds additional import/export and production controls, such as the requirement to have a licence under the PCR and permits to import/export.

6. Tadalafil and its salts — a cGMP-specific phosphodiesterase type 5 (PDE5) inhibitor. Tadalafil is a potent, selective, and reversible inhibitor indicated for the treatment of male erectile dysfunction (ED) at oral doses of 10 and 20 mg once daily. Tadalafil must be administered under the supervision of a medical practitioner.

7. Teflubenzuron — antiparasite. Teflubenzuron is indicated for the treatment of parasitic infestations caused by the developing chalimus and pre-adult stages of *Lepeophtheirus salmonis* on Atlantic salmon (*Salmo salar*). Individualized instructions, adjunctive therapy and professional monitoring by a veterinarian are required for the successful treatment of parasitic infestations.

#### *Alternatives*

The degree of regulatory control corresponds with the risk factors associated with each specific medicinal ingredient. The review of the information filed by the sponsor of these products has determined that prescription status is required at this time. Advice from a medical practitioner is necessary to ensure that consumers receive adequate risk/benefit information before taking the medication.

Any alternatives to the degree of regulatory control recommended in this regulatory initiative would need to be established through additional scientific information and clinical experience.

No other alternatives were considered.

### *Benefits and costs*

The amendment would impact on the following sectors:

— Public

Prescription access to the medicinal ingredients by project 1397 would benefit Canadians by decreasing the opportunities for improper use and by ensuring professional guidance and care.

— Health insurance plans

These medicinal ingredients, when assigned prescription status, may be covered by both provincial and private health care plans.

— Provincial health care services

The provinces may incur costs to cover physicians' fees for services. However, the guidance and care provided by the physicians would reduce the need for health care service that may result from improper use of the products. The overall additional costs for health care services should therefore be minimal.

### *Consultation*

The manufacturers affected by this proposed amendment were made aware of the intent to recommend these medicinal ingredients for inclusion on Schedule F during the review of the New Drug Submission and at the time of market approval of the drugs.

Direct notice of this regulatory proposal was provided to the provincial ministries of health, medical and pharmacy licensing bodies, and industry associations on January 5, 2004, with a 30-day comment period. This initiative was also posted on the Therapeutic Products Directorate's Web site. Two supportive responses were received.

A 75-day comment period will be provided upon prepublication in the *Canada Gazette*, Part I.

### *Compliance and enforcement*

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

*Contact*

Ms. Alexandra Bray, Policy Division, Bureau of Policy, Therapeutic Products Directorate, 1600 Scott Street, Holland Cross, Tower B, 2nd Floor, Address Locator 3102C5, Ottawa, Ontario K1A 1B6, (613) 957-6447 (telephone), (613) 941-6458 (facsimile), alexandra\_bray@hc-sc.gc.ca (electronic mail).

**PROPOSED REGULATORY TEXT**

Notice is hereby given that the Governor in Council, pursuant to subsection 30(1) ([see footnote a](#)) of the *Food and Drugs Act*, proposes to make the annexed *Regulations Amending the Food and Drug Regulations (1397 — Schedule F)*.

Interested persons may make representations with respect to the proposed Regulations 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 Alexandra Bray, Therapeutic Products Directorate, Department of Health, Address Locator 3102C5, 1600 Scott Street, 2nd Floor, Tower B, Ottawa, Ontario K1A 1B6 (Fax: (613) 941-6458; E-mail: alexandra\_bray@hc-sc.gc.ca).

Persons making representations should identify any of those representations the disclosure of which should be refused under the *Access to Information Act*, in particular under sections 19 and 20 of that Act, and should indicate the reasons why and the period during which the representations should not be disclosed. They should also identify any representations for which there is consent to disclosure for the purposes of that Act.

Ottawa, July 7, 2004

EILEEN BOYD  
*Assistant Clerk of the Privy Council*

**REGULATIONS AMENDING THE FOOD AND DRUG**

## REGULATIONS (1397 — SCHEDULE F)

### AMENDMENT

**1. Part I of Schedule F to the *Food and Drug Regulations* ([see footnote 1](#)) is amended by adding the following in alphabetical order:**

Adefovir and its salts and derivatives

*Adéfovir, ses sels et dérivés*

Almotriptan and its salts

*Almotriptan et ses sels*

Cetorelix and its salts

*Cétrorélix et ses sels*

Ketanserin and its salts

*Kétansérine et ses sels*

Phenylpropanolamine and its salts and derivatives for veterinary use

*Phénylpropanolamine, ses sels et dérivés, destinés à l'usage vétérinaire*

Tadalafil and its salts

*Tadalafil et ses sels*

Teflubenzuron

*Teflubenzuron*

### COMING INTO FORCE

**2. These Regulations come into force on the day on which they are registered.**

[Footnote a](#)

S.C. 1999, c. 33, s. 347

[Footnote 1](#)

C.R.C., c. 870

**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.



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