



Therapeutic Products Directorate
Holland Cross, Tower "B"
6th Floor, 1600 Scott Street
Address Locator # 3106B
OTTAWA, Ontario
K1A 0K9

03-123626-555

To:

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

Dear Sir/Madam:

Re: ***Food and Drug Regulations - Schedule 1397 - Schedule F Update***

This is to provide you with an opportunity to comment on the Therapeutic Products Directorate's intention to update Schedule F to the *Food and Drug Regulations* of the *Food and Drugs Act* by adding 7 medicinal ingredients to Part I of Schedule F. Once finalized, this amendment would come into force on the date of registration and approval for publication in the *Canada Gazette*, Part II.

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

.../2

The Therapeutic Products Directorate's Drug Schedule Status Committee reviews the status of chemical entities proposed for marketing. A decision regarding the necessity for prescription or other scheduled status versus nonprescription status was made for each of the drugs listed on this schedule on the basis of established and publicly available criteria. These criteria include, but are not limited to, concerns related to toxicity, pharmacological properties and therapeutic applications.

It is proposed that the following 7 substances 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 _{1B/1D} (5-HT _{1B/1D}) 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** - 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 considered also 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 PPA containing medications were used in Canada for relatively mild conditions and only provide 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, production controls e.g. requirement to have licence under PCR and permits to import/export.

6. **Tadalafil and its salts** - a potent, selective, and reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil is 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 coincides with the risk factors associated with each specific substance. The review of the information filed by the sponsor of these drugs 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 drugs by Schedule 1397 would benefit Canadians by decreasing the opportunities for improper use, and by ensuring professional guidance and care.

- **Pharmaceutical Industry**

The classification of these drugs as prescription products would make their sale subject to professional intervention, thereby reducing misuse and decreasing liability to the manufacturer.

- **Health Insurance Plans**

These drugs, 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 drugs. The overall additional costs for health care services should therefore be minimal.

Compliance and Enforcement

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

Consultation

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

This letter is being sent by email to stakeholders and is also being posted on the TPD website at http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_drugs_regulations_e.html.

Any comments regarding this proposed amendment should be addressed to Alexandra Bray, Policy Division, Policy Bureau, Therapeutic Products Directorate, 1600 Scott Street, Holland Cross, Tower 'B', 2nd Floor, Address Locator 3102C5, Ottawa, Ontario, K1A 1B6, by facsimile at 613-941-6458 or by email to alexandra_bray@hc-sc.gc.ca within **30** days.

Yours sincerely,

Robert G. Peterson, MD, PhD,
MPH
Director General