

Health Canada-Mandated Important Safety Information on
PERMAX[®] (pergolide mesylate)



August 10, 2007

Dear Health Care Professional:

Subject: Cease Sale of Permax[®] (pergolide mesylate) in Canada as of August 30, 2007

Eli Lilly Canada Inc., in collaboration with Health Canada, wishes to inform you that sales of Permax will cease in Canada as of August 30, 2007.

Subsequent to new post-market safety information coming from two papers published in the January 4, 2007 issue of the New England Journal of Medicine (NEJM) that provided further evidence consistent with previous reports of valvulopathy cases in patients taking pergolide,^{1,2} Health Canada considers that there is insufficient evidence to support the continued safe use of Permax under the current recommendations outlined in the Product Monograph. In particular, one case-controlled epidemiological study¹ found significantly higher risk of valvulopathy among patients exposed to ergot derivatives with 5-HT_{2B} agonist activity, including pergolide, compared with non-ergot dopamine agonists. Risk was greater for patients exposed to pergolide longer than six months. Risk was especially elevated at daily pergolide doses exceeding 3 mg; risk elevation was present but less marked at daily doses below 3 mg. A second study utilizing echocardiography, found that valvular abnormalities (sometimes asymptomatic) were common among pergolide-treated patients. In this study mean pergolide dose was 2.8 mg/day and valvulopathy risk increased with cumulative pergolide exposure.²

- Manufacturer sales of Permax will be ceased in Canada as of August 30, 2007.
- Patients using Permax should be transitioned to an alternative anti-Parkinson therapy at the earliest medically feasible point.
- No new patients should be started on Permax.
- To discontinue treatment with Permax, gradual reduction in Permax dosage over several weeks, as per the Product Monograph instructions, is recommended to prevent recurrence of symptoms of the underlying condition and serious adverse events associated with abrupt discontinuation (e.g. neuroleptic malignant syndrome-like symptoms, hallucinations, and confusion).
- Transition strategy should be individualized to each patient.
- Pharmacies may continue to dispense existing Permax supplies to allow for a transition period to switch patients to an alternative medication.
- Once the cease sale is in effect, Permax may be made available through the Health Canada Special Access Programme to individual patients who have failed to respond to alternative therapies.

Background Information:

Permax[®] (pergolide mesylate) is a dopamine agonist used in the treatment of the signs and symptoms of idiopathic Parkinson's disease. It is indicated for use both as early therapy, without concomitant levodopa, and as an adjunct to levodopa (usually with a peripheral decarboxylase inhibitor).

Since Permax was first launched in Canada in 1991, retroperitoneal, pleural, and pericardial fibrosis have been recognized as rare adverse events reported with Permax. Since 2002, reports of cardiac valvulopathy have been reported in association with Permax use. The Permax Product Monograph was modified accordingly over the years to reflect emerging post-market information. These safety findings were also previously communicated to Canadian healthcare professionals in April 2003 and October 2004. These communications can be viewed online at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2003/lilly_permax_hpc-cps_e.html and http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2004/shire_permax_2_hpc-cps_e.html

In light of the additional post-market safety information from the NEJM studies, Health Canada considers that there is insufficient evidence to support the continued safe use of Permax under the current recommendations outlined in the Product Monograph. Thus, in cooperation with Health Canada, Eli Lilly Canada will stop distribution and sales of Permax as of August 30, 2007.

Advice for discontinuation and transition to alternative medications for patients currently taking Permax:

Patients using Permax should be advised that Permax sales will be ceased by the manufacturer as of August 30, 2007 and should be transitioned to an alternative anti-Parkinson medication at the earliest medically feasible point. Healthcare professionals are requested to facilitate access for these patients, to establish appropriate treatment plans and ensure that each patient has an adequate supply of Permax for safe discontinuation.

To discontinue treatment with Permax, gradual reduction in Permax dosage over several weeks, as per the Product Monograph, is recommended to prevent both the recurrence of symptoms of the underlying condition and the exacerbation of potentially serious side effects experienced with abrupt discontinuation (e.g. hallucinations, confusion, and neuroleptic malignant syndrome-like symptoms).

Although there is no formal protocol for transitioning patients from one anti-Parkinson medication to another, information is available in the scientific literature reviewing the techniques commonly employed in clinical practice and the important factors that should be considered for transition between anti-Parkinson medications. The transition techniques include cross-tapering (gradual down-titration of the current medication while up-titrating the new medication) and overnight switching to another dopamine agonist. If switching overnight, equivalent doses of dopamine agonists should be used.³⁻⁷

The choice of transition strategy and its detailed execution must be individualized for each patient. Prescribers are advised to pay specific attention to any potentially significant adverse events when selecting and switching to an alternative anti-Parkinson medication.

Access to Permax after cease sale is in effect

While further sales of Permax by the manufacturer will be prohibited after August 30, 2007, pharmacies may continue to dispense existing supplies to allow for a transition period to switch patients to an alternate therapy. Eli Lilly Canada Inc. and Health Canada anticipate there will be sufficient supplies in pharmacies to allow adequate transition to another product. Should pharmacy supplies be inadequate and/or patients cannot be safely transitioned to marketed alternatives, prescribers should contact the Special Access Programme at Health Canada to request temporary access to the drug for individual patients.

In most cases, alternative therapies are available to treat Parkinson's Disease. Availability of Permax through the Special Access Programme may be an option for patients who have failed to respond to alternative therapies, or for whom a neurologist experienced in the treatment of movement disorders can justify the use of Permax in view of the increased risk of cardiac valvulopathy. Information on the Special Access Programme is available at:

http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogués/sapfs_pasfd_2002_e.html

Reporting of Adverse Events

Managing marketed health product-related adverse reactions depends on the diligence of healthcare professionals and consumers to report them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of cardiac valvulopathy or other serious or unexpected adverse reactions in patients receiving Permax[®], should be reported to Eli Lilly Canada or Health Canada at the following addresses:

Customer Response Centre
Eli Lilly Canada Inc.
3650 Danforth Avenue
Toronto, Ontario, M1N 2E8
Tel.: 1-888-545-5972
Fax: 1-888-898-2961

Any suspected adverse reaction can also be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate

HEALTH CANADA

Address Locator: 0701C

OTTAWA, Ontario, K1A 0K9

Tel: (613) 957-0337 or Fax: (613) 957-0335

To report an Adverse Reaction, consumers and health professionals may call toll free:

Tel: 866 234-2345

Fax: 866 678-6789

cadrmp@hc-sc.gc.ca

The [AR Reporting Form](#) and the [AR Guidelines](#) can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/ar-ei_form_e.html

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/ar-ei_guide-ldir_e.html

For other inquiries related to this communication, please contact Health Canada at:

Marketed Health Products Directorate (MHPD)

E-mail: MHPD_DPSC@hc-sc.gc.ca

Tel: (613) 954-6522

Fax: (613) 952-7738

This communication can be viewed online at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/index_e.html.

Thank you for your attention to this important safety matter.

Should you have any questions about Permax, please contact the Eli Lilly Canada Customer Response Centre at 1-888-545-5972.

Sincerely,



Loren D. Grossman, MD, FRCPC, FACP
Vice-President, Research and Development
Eli Lilly Canada Inc.

PERMAX[®] is a registered trademark of Eli Lilly and Company

References:

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2. Zanettini R, Antonini A, Gatto G, et al. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007;356:39-46.
3. Hanna PA, Ratkos L, Ondo WG, Jankovic J. Switching from pergolide to pramipexole in patients with Parkinson's disease. *J Neural Trans* 2001;108:63-70.
4. Goetz CG, Blasucci L, Stebbins GT. Switching dopamine agonists in advanced Parkinson's disease: Is rapid titration preferable to slow? *Neurology* 1999;52:1227-1229.
5. Canesi M, Antonini A, Mariani CB, et al. An overnight switch to ropinirole therapy in patients with Parkinson's disease. *J Neural Transm* 1999;106:925-929.
6. Grosset K, Needleman F, Macphee G, Grosset D. Switching from ergot to nonergot dopamine agonists in Parkinson's disease: A clinical series and five-drug dose conversion table. *Mov Disord* 2004;19(11):1370-1374.
7. Thobois S. Proposed dose equivalence for rapid switch between dopamine receptor agonists in Parkinson's disease: A review of the literature. *Clin Therapeut* 2006;28(1):1-12.