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Health Products and Food Branch
Direction générale des produits de santé et des aliments

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This is duplicated text of a letter from **Shire BioChem Inc.**
Contact the company for a copy of any references, attachments or enclosures.

**Health Canada Endorsed Important Safety Information on
Adderall XR**



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www.shire.com

August 31, 2005

Subject: ADDERALL XR and serious adverse events

Dear Health Care Professional,

Shire BioChem Inc., after discussions with Health Canada, wishes to advise Canadian healthcare providers of the return of Adderall XR™ (mixed salts amphetamine extended release capsules) to the Canadian market for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The Canadian Product Monograph will be revised as previously proposed by Shire BioChem in November 2004. The proposed text includes warnings about the misuse of Adderall XR, and that Adderall XR generally should not be used in patients with structural cardiac abnormalities.

Adderall XR was suspended from the Canadian market by Health Canada on February 9, 2005, due to concerns that use of Adderall may have been associated with an increased risk of sudden/cardiac death, and stroke in children and adults taking the usual recommended doses, based on a preliminary review of international data. There have been no Canadian reports of death in patients using Adderall XR.

This decision has subsequently been re-assessed by Health Canada following the recommendations of an independent [New Drug Committee](#) appointed by Health Canada at the request of Shire BioChem, after review of safety data and analyses presented by both Shire BioChem and Health Canada. This Committee was comprised of a pediatric cardiologist, a consultant physician specializing in pediatric developmental and behavioural disorders, and was chaired by a pharmaco-epidemiologist. This reassessment involved a comprehensive review of:

- a) sudden/cardiac death and stroke in the general population and,
- b) comparative pharmacoepidemiological analyses of the event reporting rates for Adderall versus other ADHD drugs.

The conclusions from this re-assessment included the following:

- **Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although not proven, healthcare professionals should be advised of this potential.**
- **There is insufficient evidence to support the belief that there is an increased risk of sudden/cardiac death or stroke with Adderall compared to other ADHD treatments.**

Sudden / Cardiac Death in Children

In the general pediatric population, potential risk factors for sudden unexplained or cardiac death include, but are not limited to, cardiac abnormalities that may be undiagnosed, positive family history of sudden death at a young age, or ventricular arrhythmias.

It is recognized that there is a theoretical potential for all drugs used in the management of ADHD to increase the risk of sudden/cardiac death. Whether this increased risk is similar to the undertaking of exercise or other strenuous activities in the general population, or is dependent upon underlying predisposing congenital or acquired cardiac risk factors is uncertain.

Shire BioChem has been informed that Health Canada, at the recommendation of the New Drug Committee, will seek expert consultation on the appropriateness of potential additional cautions (e.g., strenuous exercise, use of other stimulants, family history of sudden/cardiac death) in patients treated with any ADHD drug (stimulant or non-stimulant) that might be considered in the assessment of benefit versus risk for an individual patient.

Product Monograph Changes

As recommended by the [New Drug Committee](#), Health Canada is approving the revision of the Canadian Product Monograph as previously proposed by Shire BioChem in November 2004, which includes the addition of the following warnings:

- Sudden death has been reported with amphetamine treatment at therapeutic doses in children with structural cardiac abnormalities;
- Adderall XR should generally not be used in patients with pre-existing structural cardiac abnormalities.
- Misuse of amphetamines may cause serious cardiovascular adverse events including sudden death.

In addition, myocardial infarction, sudden death and stroke have been added to the list of reported adverse events.

Please refer to the attached Product Monograph revisions for future reference.

Reporting of Adverse Events

The reporting rate for sudden/cardiac death and stroke in patients taking Adderall, as with other

psychostimulant drugs, is less than the actual incidence in the unexposed population. However, as with all drugs, underreporting of post-marketing adverse reaction reports makes it difficult to compare reporting rates and actual incidences.

The identification, characterization, and management of marketed health product-related adverse reactions are dependent on the active participation of healthcare professionals in adverse drug reaction reporting programs. Any occurrences of cardiac or sudden death or stroke or any other serious and/or unexpected adverse reactions in patients receiving Adderall XR should be reported to Shire BioChem or Health Canada at the following addresses:

Shire BioChem Inc.
2250 Alfred-Nobel Blvd.
Suite 500, Saint-Laurent
Quebec, H4S 2C9
Tel: 1-800-268-2772
Fax: (514) 787-2426

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

cadmp@hc-sc.gc.ca

For other inquiries, please refer to contact information:

Bureau of Cardiology, Allergy and Neurological Sciences

BCANS_Enquiries@hc-sc.gc.ca

Tel: (613) 941-1499

Fax: (613) 941-1668

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

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Should you have any questions regarding Adderall XR or require a copy of the revised Adderall XR Product Monograph, please contact Shire BioChem's medical information department at 1-800-268-2772.

Sincerely,

Original signed by

Bonnie Cockhill
Director, Scientific Affairs

ADDERALL XR™
Product Monograph Revisions - August 2005

ADDITIONAL WARNINGS:

Misuse and Serious Cardiovascular Adverse Events

The misuse of amphetamines may cause serious cardiovascular adverse events and sudden death.

Pre-existing Structural Cardiac Abnormalities and Sudden Death

Sudden death has been reported with amphetamine treatment at therapeutic doses in children with structural cardiac abnormalities. ADDERALL XR™ (mixed salts amphetamine extended-release capsules) generally should not be used in patients with structural cardiac abnormalities.

ADDITIONAL ADVERSE REACTIONS:

Cardiovascular System: sudden death, myocardial infarction, stroke

Nervous System: seizures

ADDITIONAL INFORMATION FOR THE CONSUMER:

Before using ADDERALL XR™

*Tell the doctor if you / your child has one or more of the following conditions:**

..., structural heart abnormalities, ...

Other important safety information

*Abuse of amphetamine can lead to dependence** and possibly serious heart problems and death.

* text in italics represents previously existing text.