NOTICE TO HOSPITALS
Health Canada Issued Important Safety Information on methylene blue injectable

February 16, 2011

To: Hospital Chief of Medical Staff

Please distribute to Departments of Pharmacy, Surgery, Anaesthesia, Emergency Medicine, Internal Medicine, Intensive Care and **post this Notice** in your institution

Subject: Association of serotonin toxicity with methylene blue injectable in combination with serotonin reuptake inhibitors

Health Canada would like to inform you that cases of serotonin toxicity have been reported and published in association with the use of methylene blue injectable in patients exposed to drugs with serotonin reuptake inhibition properties e.g. selective serotonin reuptake inhibitors (SSRIs). The cases of serotonin toxicity (also known as serotonin syndrome) involved agitation or diaphoresis or hypertonia accompanied with pyrexia (> 38° C), and tremor, hyperreflexia or clonus (spontaneous, inducible or ocular).

Health Canada will be working with the market authorization holders of methylene blue injectable products to update the Canadian prescribing information for this agent to include the following points:

- Serotonin toxicity/serotonin syndrome has been reported when methylene blue was administered intravenously in patients also receiving other drugs with serotonin reuptake inhibition properties. Several of these cases required admission to intensive care unit.

- If drugs with serotonin reuptake inhibition properties are being taken, careful consideration needs to be given to stop them before methylene blue injectable use to allow a washout period equivalent to at least 4-5 half-lives.

Recent research has revealed that methylene blue has structural properties similar to monoamine oxidase inhibitors (MAOI), known precipitants of serotonin toxicity when administered concomitantly with drugs having serotonin reuptake inhibition properties. Serotonin toxicity has been reported when methylene blue was administered intravenously at concentrations as low as 1 mg/kg, in patients receiving selective serotonin reuptake inhibitors (SSRIs) or other drugs with serotonin reuptake inhibition properties (e.g., duloxetine, venlafaxine and clomipramine). Several of these cases required admission to the intensive care unit.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on

the basis of spontaneously reported post-market adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any cases of serotonin syndrome or serotonin toxicity or other serious or unexpected adverse reactions in patients receiving methylene blue injectable should be reported to Health Canada.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario K1A 0K9

The Reporting Forms, postage paid labels, and Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php). The Reporting Form is also in the *Canadian Compendium of Pharmaceuticals and Specialties.*

For other health product inquiries related to this communication, please contact Health Canada at:
Lead Directorate: Marketed Health Product Directorate
E-mail: mhpd_dpsc@hc-sc.gc.ca
Telephone: 613 954-6522
Fax: 613 952-7738