IMPORTANT NEW SAFETY INFORMATION: HEPATIC INJURY ASSOCIATED WITH BETA-INTERFERON TREATMENT FOR MULTIPLE SCLEROSIS

December 4, 2003

Dear Health Care Professional:

Health Canada, in association with Biogen Idec Canada, Inc., Berlex Canada, Inc., and Serono Canada, Inc., would like to inform you of updated safety information from post-marketing experience with beta-interferon therapy for multiple sclerosis (MS).

Rare post-market cases of serious hepatic injury, including autoimmune hepatitis, hepatitis, and hepatic failure, have been reported with beta-interferon treatment for MS.

It is recommended that liver function testing occur at baseline, every month for the first 6 months of treatment, and at 6 month intervals thereafter. Dose reduction or discontinuation of therapy should be considered if alanine aminotransferase (ALT) levels increase 5 times above the upper limit of normal.

Three (3) worldwide cases of hepatic failure requiring liver transplantation have been reported, one of which is Canadian. The Canadian case reported the concomitant use of a drug known to have hepatotoxic effects, therefore caution must be exercised when prescribing drugs with documented hepatotoxicity to patients on beta-interferon therapy for MS.

Beta-interferon therapy should be initiated with caution in patients with a history of significant liver disease, alcohol abuse, and patients with clinical evidence of active liver disease.

The table below describes all beta-interferon products marketed in Canada for MS as well as specific dosage and administration information:

Product:	Company:	Dosage and Administration:
AVONEX (Interferon beta-1a)	Biogen Idec Canada, Inc.	30 mcg weekly; intramuscular
BETASERON (Interferon beta-1b)	Berlex Canada, Inc.	0.25 mg every other day; subcutaneous
REBIF (Inteferon beta-1a)	Serono Canada, Inc.	22 mcg or 44 mcg three times per week; subcutaneous

The reported occurrence of post-market cases of serious hepatic injury associated with the beta-interferons is rare (defined as a reporting rate of between 1/1,000 and 1/10,000 patient-years of exposure). In addition to post-marketing cases, serious hepatotoxicity has been reported in the literature for all beta-interferon products, including a Canadian case of hepatic failure requiring liver transplantation[1-5]. A total of 3 such hepatic failure cases requiring liver transplantation have been reported worldwide with beta-interferon products.

Post-marketing experience with the beta-interferon class has shown that serious hepatic injury occurs predominantly in the first 6 months of therapy, however cases have been reported in patients on therapy beyond 1 year. It is therefore recommended that liver function testing be conducted monthly for the first 6 months of therapy with monitoring every 6 months thereafter in the absence of symptoms. Upon initiating beta-interferon therapy, physicians are advised to educate patients on the signs and symptoms of hepatic injury, including jaundice, diffuse itching, nausea and vomiting, and easy bruising of the skin. Patients should be instructed to immediately contact their physician should these signs and symptoms occur.

Dose reduction or discontinuation of beta-interferon therapy should also be strongly considered if ALT levels increase 5 times above the upper limit of normal.

Reporting rates determined on the basis of spontaneously reported post-marketing adverse events are generally presumed to underestimate the risks associated with drug treatments. The identification, characterization, and management of drug-related adverse events are dependent on the active participation of health care professionals in adverse drug reaction reporting programmes.

Health care professionals are asked to report any suspected adverse reactions in patients receiving beta-interferons to the relevant companies at the following addresses:

AVONEX®:
Biogen Idec Canada Inc.
3 Robert Speck Parkway, Suite 300
Mississauga, ON
L4Z 2G5
Tel: (905) 897-3234
Fax: (905) 897-3222
Attention: Medical Services

BETASERON®:
Berlex Canada, Inc.
334, avenue Avro
Pointe Claire, QC
H9R 5W5
Tel: (800) 361-0240
Fax: (514) 782-2243

REBIF®:
Serono Canada, Inc.
1075 North Service Road West
Suite 100
Oakville, Ontario
L6M 2G2
Tel: (888) 737-6668
Fax: (905) 825-3209

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.

Sincerely,

original signed by	***original signed by***	***original signed by***
Adel Gehshan, M.D. Senior Director Biogen Idec Canada, Inc.	Alexander Ruebig, M.D., PhD. Vice President, Scientific Affairs Berlex Canada, Inc.	Mona Salesse Director, Regulatory Affairs Serono Canada, Inc.

Avonex® is a registered trademark of Biogen Idec Inc.
Betaseron® is a registered trademark of Schering AG.
Rebif® is a registered trademark of Serono, Inc.

References:

1. Durelli L. 1998. Interferon treatment for multiple sclerosis: autoimmune complications can be lethal. Neurology. 50: 570-571.
2. Duchini A. 2002. Autoimmune hepatitis and Interferon Beta-1a for Multiple Sclerosis. Am J Gastroenterol. 97: 767-768.
3. Yoshida EM et al. 2001. Fulminant hepatic failure during interferon beta treatment for multiple sclerosis. Neurology 56(10): 1416.
4. Yoshida EM et al. 2001. Erratum: Fulminant hepatic failure during interferon beta treatment for multiple sclerosis. Neurology 57(11): 2153.
5. Francis GS et al. 2003. Hepatic reactions during treatment of multiple sclerosis with interferon-b-1a, incidence and clinical significance. Drug Safety 26(11): 815-827.

Any suspected adverse reactions can also be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0201C2
OTTAWA, Ontario, K1A 1B9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll free for consumers and health professionals:
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 TPD web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.