April 10,2003

IMPORTANT DRUG SAFETY INFORMATION ABOUT DIANE®-35 AND THE RISK OF VENOUS THROMBOEMBOLISM

- DIANE®-35, as with all estrogen/progestogen combinations, is **contraindicated** in women with thrombophlebitis, thromboembolic disorders, or a history of these conditions.
- DIANE®-35 users appear to have an **elevated risk of venous thromboembolic events** compared to users of combination oral contraceptives in some published studies.
- DIANE®-35 should **not** be prescribed for the purpose of contraception alone.
- During treatment with DIANE®-35, other oral contraceptives should not be used.

Dear Health Care Professional(s),

Berlex Canada Inc., following discussions with Health Canada, would like to inform you about recent published information on the risk of venous thromboembolism (VTE) with DIANE®-35 (cyproterone acetate and ethinyl estradiol). DIANE®-35, like all estrogen/progestogen combinations, is associated with an increased risk of VTE compared with no use.

DIANE®-35 is a therapeutic agent indicated for the treatment of women with severe acne, unresponsive to oral antibiotic and other available treatments, with associated symptoms of androgenization, including seborrhea and mild hirsutism. It should be discontinued 3 to 4 cycles after signs have completely resolved. DIANE®-35 has many properties in common with combination oral contraceptives and the same contraindications, warnings and precautions apply to DIANE®-35.

Based on an independent analysis, commissioned by Berlex, of recently published information[1-7], cases of non-fatal VTE ranging in incidence from 1.2 to 9.9 events per 10,000 women-years have been observed in users of DIANE®-35. As context, the incidence of VTE in non-users of any oral contraceptive is estimated to be 0.5 to 1 event per 10,000 women-years, and increases to 4 events per 10,000 women-years in long-term users of low estrogen content (< 50 µg ethinyl estradiol) combination oral contraceptives[8]. These event rates are rare, but still justify caution in the use of DIANE®-35.

Since market introduction in 1998, Health Canada has received 11 reports of VTE (deep vein thrombosis, pulmonary embolism, and stroke) equivalent to a reporting rate of 0.33 events per 10,000 women-years. One of these cases involved a death. It should be noted that reporting rates determined on the basis of spontaneously reported post-marketing adverse events are generally presumed to underestimate the risks associated with drug treatments.

Women with androgen-related conditions (e.g., severe acne or hirsutism) may have an inherently increased cardiovascular risk. The excess risk of VTE is highest during the first year a woman ever uses a combination oral contraceptive.

Berlex Canada Inc. is committed to providing you with the most current product safety information on its products. We hope this information will be helpful to you in caring for your patients on DIANE®-35. The official DIANE®-35 Product Monograph is being updated to reflect this new information.

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 DIANE®-35 directly to Berlex Canada Inc. at the following address:

Berlex Canada Inc.
334 Avro Avenue
Pointe-Claire, Quebec
H9R 5W5
Tel: (800) 361-0240 or by fax at (514) 631-4721

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.

If you have any questions regarding DIANE®-35, please contact Berlex Canada at 1-800-361-0240.

Yours sincerely,

original signed by

Dr. Jean-Louis Stril, M.D.
Manager, Disease Management and Drug Safety
Berlex Canada Inc.

[1] Lidegaard O. et al. Contraception 2002; 65:187-196.
[2] Pini M et al. Rec Prog Med 1996; 87:331-337.
[3] Farmer RDT et al. Br J Clin Pharmacol 2000; 49:580-590.
[4] Vasilakis-Scaramozza C and Jick H. The Lancet 2001; 358:1427-1429.
[5] Seaman HE et al. Human Reproduction 2003; 18:522-526.
[6] WHO 1995 Lancet 1995; 346:1582-1588.
[7] Farmer RDT. Hum Rep Upd 1999; 5:688-706.
[8] The European Agency for the Evaluation of Medicinal Products (EMEA). EMEA committee for proprietary medicinal products (CPMP) Public Assessment Report. Combined oral contraceptives and venous thromboembolism. 28 September 2001. http://www.emea.eu.int/pdfs/human/regaffair/0220101en.pdf

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*.