



The Society of Obstetricians
and Gynaecologists of Canada
La Société des obstétriciens
et gynécologues du Canada



Canadian Dermatology Association
Association canadienne de dermatologie



Federation of Medical
Women of Canada
Fédération des femmes
médecins du Canada



CANADIAN
PHARMACISTS
ASSOCIATION

ASSOCIATION DES
PHARMACIENS
DU CANADA

Ottawa, June 30, 2005

RE: DIANE® 35 Health Canada Public Advisory

Dear Members and Colleagues:

The following information regarding DIANE® 35 (cyproterone acetate 2mg and ethinyl estradiol 35 µg), relates to the Health Canada Public Advisory issued May 12 2005¹.

The Society of Obstetricians and Gynaecologists of Canada (SOGC) and its partners, the Canadian Dermatology Association, the Federation of Medical Women of Canada and the Canadian Pharmacists Association, would like to reiterate the scientific evidence surrounding the usage and safety of DIANE® 35 (CPA/EE). DIANE® 35 is a therapeutic agent indicated for the treatment of women with severe acne, unresponsive to oral antibiotics and other available treatments with associated symptoms of androgenization, including seborrhoea and mild hirsutism. This latest advisory is intended simply to inform the public that a new version of the product monograph of DIANE® 35 has been issued and that it contains the same warnings previously issued Dec 19th, 2002² and Apr 10th 2003³. However it appears to have left physicians and consumers once again wondering about the safety of DIANE® 35.

DIANE® 35 is not indicated for the use as an oral contraceptive alone and should not be prescribed as a contraceptive. However, when taken as recommended for the approved indication, it will provide reliable contraception. Women taking DIANE® 35 should not be prescribed an additional hormonal contraceptive.

The incidence of venous thromboembolism (VTE) in non-users of oral contraceptives is estimated to be 4 events per 100,000 women-years, and increases to 10 to 15 events per 100,000 women-years with the use of second-generation oral contraceptives containing levonorgestrel. The risk of VTE in pregnancy has been estimated at 60 events per 100,000 pregnancies. Women with androgen-related conditions who are prescribed DIANE® 35 (e.g. women with severe acne, hirsutism and seborrhoea) may have an inherently increased risk for thromboembolic events⁴.

A best evidence synthesis of worldwide literature reported by Spitzer in JOGC 2003⁵ clearly showed that the risks of VTE among CPA/EE users do not exceed the risks of VTE among conventional OC users. A more recent report published by Seaman et al⁶ came to the conclusion that the risk of VTE associated with CPA/EE use did not differ significantly from that associated with the use of conventional oral contraceptives. This key point took into consideration that acne and/or hirsutism are common complaints among women with polycystic ovarian syndrome (PCOS). PCOS itself is also associated with an adverse

cardiovascular risk profile. This issue of confounding was addressed rigorously and subsequent risk estimates indicated that the risk of VTE with CPA/EE use was not significantly greater than that risk in women prescribed conventional OCs. This study also highlights the complexity of associating VTE with women prescribed CPA/EE and emphasises the need to adequately adjust for confounding in risk assessment analyses.

Alternative therapies such as isotretinoin recommend women to adhere to two methods of contraception and carries significant risks of congenital anomalies if pregnancy ensues.

We have attached for your use an updated fact sheet on DIANE® 35 to distribute to your patients who may have concerns about the medication. The references from the Farmer, Spitzer and Seaman studies and all previous health advisories mentioned are included. This information is also available on the SOGC website at www.sogc.org. We hope that this update will be of assistance to you and your patients and help clarify the new Health Canada Public Advisory issued May 12th, 2005.

Summary and recommendation:

DIANE® 35 is an effective and safe product used to treat severe acne and is the preferred treatment in women who require contraception. DIANE® 35 does not have to be discontinued and can be safely prescribed if well tolerated and deemed necessary by the physician. Duration of therapy should be determined on a case to case basis. Repeated "Stop-start" regimens are not an optimal strategy for treating androgen dependent disorders. Treatment can be continued for a longer period of time in a patient who demonstrates no serious side effects.

Should you have any other comments or questions, do not hesitate to contact one of the associations listed below.

Yours sincerely,



Michael Elias Helewa, MD
President, SOGC



Danielle Marcoux, MD
President, CDA



Cathy Younger-Lewis, MD
President, FMWC



George Murray
President, CPhA

References:

- 1 Health Canada Advisory Panel 2005 (Included as attachment)
- 2 Health Canada Advisory Panel 2002 (Included as attachment)
- 3 Health Canada Advisory Panel 2003 (Included as attachment)
- 4 Farmer D.J. et al, Journal of Obstetrics and Gynaecology, 1995,15:195-200
- 5 Spitzer W. O., Journal of Obstetrics and Gynaecology Canada, 2003, 25(12):1011-8
- 6 Seaman et al, Pharmacoepidemiology and Drug Safety 2004; 13: 427-436