

## Scrutiny of Diane-35 due to potential dangers of off-label prescribing

When Anne Rochon Ford mentions the potential dangers of a drug sometimes used for birth control to groups of women, she scans the room and watches the faces drop. They are the ones, she figures, who are using it.

“It’s not as popular as in the 1990s,” says Rochon Ford. “But it is still being used.”

That product — cyproterone acetate and ethinyl estradiol, commonly known as Diane-35 — is under intense scrutiny in many countries, including Australia and Canada. One of its adverse effects is thromboembolism, such as deep venous thrombosis, pulmonary embolism, stroke or myocardial infarction. Of course, this has been known for many years.

More recently, France issued a three-month advertising ban for Diane-35 and its generic equivalents after reviewing 25 years of data and linking four deaths to the drug. Now other countries are reassessing its safety and the European Medicines Agency has initiated a Europe-wide review.

Health Canada is also re-examining the drug. “When a foreign regulator takes action on a drug, it prompts a new review of the drug by Health Canada to account for any new information that may be available and to review information in the Canadian context with respect to drug indication and use in Canada,” Judith Gadbois-St-Cyr, a media relations officer with Health Canada, writes in an email.

The standard timeline for such a review is 60 days, notes Gadbois-St-Cyr, though this one will be conducted in an “expedited manner” and Health Canada will “take appropriate action as necessary once the review is complete.” Since 2000, the deaths of 11 Canadians aged 15–46 have been linked to the drug, according to 200 Health Canada adverse reaction reports recently obtained by the *Toronto Star*. Those women, eight of whom were under age 30, experienced



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**Some young women may have chosen Diane-35 for the “2-for-1” convenience of tackling both birth control and acne.**

various complications prior to their deaths, including blood clots in their legs, chest pain, bleeding in their brains or blockages in their lungs.

Cases of venous thromboembolism in women taking combination oral contraceptives date back to the 1960s. But in a study of about 100 000 women in the United Kingdom, it was found to be four times as likely to occur in those taking the progestin used in Diane-35, cyproterone, compared to the alternative levonorgestrel (*Contraception* 2002; 65:187-96).

The biggest problem with Diane-35, according to Rochon Ford, is that it became widely used for contraception though it was created and tested to treat severe acne. And it’s supposed to be used only for short periods.

“Women don’t go on birth control for six months,” says Rochon Ford. “They go on it for years.”

In Canada, it is approved only to treat severe acne in women who are unresponsive to other treatments. “Diane-35 is not, and has never been, indicated as

an oral contraceptive,” Gadbois-St-Cyr writes in an email. “The benefits of Diane-35 currently outweigh its known risks when used according to the authorised indication.”

The authorized uses of Diane-35 differ across Europe. Some countries have approved it as a contraceptive for women with hormone-related issues, such as alopecia or excessive growth of facial hair.

The drug is authorized only as an acne treatment in France, though the country’s medical regulator, Agence Nationale de Sécurité du Médicament et des Produits de Santé, has noted widespread off-label use as birth control. About 325 000 women in France used Diane-35 last year, according to the agency, which also noted that the drug is sold in more than 116 countries.

The off-label popularity of the drug may have been a product of marketing, the “2-for-1” convenience of tackling acne and birth control, clever packaging that resembles birth control pills, too much prescribing by physicians or

the influence of friends on young women making their first choices about birth control.

“You carry it around in your backpack. It has a cool name. It became a peer pressure thing,” says Rochon Ford.

Off-label prescribing can be done safely and effectively with some drugs, suggests Rochon Ford, but this is an example of when the practice can lead to harm. “This raises serious issues about how particular drugs in off-label prescribing situations are more danger-

ous than others. This drug is a red flag.”

When used to treat severe acne, as approved by Health Canada, Diane-35 has a “favourable benefit–risk profile,” according to the drug’s manufacturer Bayer Inc. Canada. The company claims it is unaware of any new scientific evidence that would lead it to alter that assessment.

“Bayer fully stands behind Diane-35,” Marija Mandic, head of communications for Bayer Inc. Canada, writes in an email.

“At Bayer we take the safety of our products very seriously and we continuously review the safety profiles of our products worldwide. Bayer investigates reports on side effects thoroughly, and collaborates closely with the respective national authorities, including Health Canada, in accordance with statutory requirements concerning the use and the benefit–risk profile of Diane-35.”  
— Roger Collier, *CMAJ*

*CMAJ* 2013. DOI:10.1503/cmaj.109-4414