

**Updated December 1, 2011**

**Bayer Inc. Medical Statement**

**Safety of Hormonal Combined Oral Contraceptives (YAZ<sup>®</sup>, Yasmin<sup>®</sup>)**

Large prospective studies have confirmed that the risk for venous thromboembolism (VTE) with drospirenone-containing combined oral contraceptives (COCs), including YAZ<sup>®</sup> and Yasmin<sup>®</sup>, is comparable to the risk of VTE with other low dose ( $\leq 35 \mu\text{g}$  ethinylestradiol) COCs.<sup>1,2</sup>

YAZ<sup>®</sup> and Yasmin<sup>®</sup> are the only COCs licensed in Canada containing drospirenone, a progestin with antimineralecorticoid activity.<sup>3,4</sup>

An increased risk of thromboembolic and thrombotic disease associated with the use of all COCs, including YAZ<sup>®</sup> and Yasmin<sup>®</sup>, is well-established and is reflected in the respective prescribing information of all COC products. The risk of VTE in women, who take low-dose COCs including YAZ<sup>®</sup> and Yasmin<sup>®</sup>, is lower than the risk for VTE associated with pregnancy and delivery.

Bayer's oral contraceptives have been and continue to be extensively studied worldwide and for most healthy women of reproductive age, the benefits of COCs will outweigh the risks when used as directed.

Bayer has sponsored several large, prospective, independently conducted, observational studies in Europe and the United States including EURAS<sup>1</sup> and Ingenix<sup>2</sup>. These studies of more than 120,000 oral contraceptive users confirmed that women taking low-dose oral contraceptives have similar VTE risk regardless of the progestin used. The results of the EURAS and Ingenix studies, which were published in 2007, offer important information about the safety of oral contraceptives as typically used.

All of the currently available data from these studies show that:

- VTE is a rare event in women who take low-dose oral contraceptives.
- The risk for venous thrombosis in women who take low-dose oral contraceptives is lower than the risk associated for VTE with pregnancy and delivery<sup>5</sup>.
- Two prospective studies, EURAS and Ingenix, that together enrolled 125,961 women for a total of 184,000 woman years, demonstrated that among the progestins studied, including levonorgestrel and drospirenone, the risk of VTE was comparable.

Retrospective studies (Lidegaard et al.<sup>6</sup>, Lidegaard et al.<sup>7</sup>, van Hylckama Vlieg et al.<sup>8</sup>, Jick and Hernandez<sup>9</sup>, Parkin et al.<sup>10</sup> and Gronich et al.<sup>11</sup>) suggest that the VTE risk in Yasmin<sup>®</sup> users was higher than the risk associated with levonorgestrel-containing COCs. The results of these retrospective studies are not consistent with the large amount of data generated in Yasmin<sup>®</sup> and YAZ<sup>®</sup> clinical and post-marketing studies. All of these retrospective studies have significant methodological issues inherent in their study designs<sup>12, 5</sup> that raise important questions about the validity of the conclusions drawn by the authors.

COCs are one of the most convenient, safe and reliable options available to women to prevent unplanned pregnancies. Risk factor information is important in deciding whether a COC is a suitable contraceptive choice for an individual woman.



Shurjeel H. Choudhri MD, FRCPC  
Senior Vice President and Head, Medical and Scientific Affairs  
Bayer Inc.

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- <sup>1</sup> Publication of the EURAS data: Dinger et al.: The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. In: *Contraception*, 75, 2007, 344 – 354.
  - <sup>2</sup> Publication of the INGENIX data: Seeger et al.: Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. In: *Obstetrics & Gynecology*, Vol. 110, No. 3, September 2007, 587 – 593.
  - <sup>3</sup> Apter et al., Effect of an oral contraceptive containing drospirenone and ethinylestradiol on general well-being and fluid-related symptoms. In: *The European Journal of Contraception and Reproductive Health Care*, 8, 2003, 37 – 51.
  - <sup>4</sup> Parsey and Pong. An open-label, multicenter study to evaluate Yasmin, a low-dose combination drospirenone, a new progestogen. In: *Contraception*, 61, 2000, 105 – 111.
  - <sup>5</sup> Reid et al. Oral contraceptives and the risk of venous thromboembolism: an update. In: *J Obstet Gynaecol Can*, Vol. 32, No. 12, 2010, 1192 – 1197.
  - <sup>6</sup> Lidegaard , Løkkegaard , Svendsen , Agger. Hormonal contraception and risk of venous thromboembolism: national follow-up study. In: *BMJ* 2009;339:b2890.
  - <sup>7</sup> Lidegaard ,Nielsen, Skovlund etl. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study 2001-9. In: *BMJ* 2011;343: d6423
  - <sup>8</sup> van Hylckama Vlieg, Helmerhorst, Vandenbroucke, Doggen, Rosendaal. Effects of oestrogen dose and progestogen type on venous thrombotic risk associated with oral contraceptives: results of the MEGA case-control study. In: *BMJ* 2009;339:b2921.
  - <sup>9</sup> Jick, Hernandez, Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. In: *BMJ* 2011;340:d2151.
  - <sup>10</sup> Parkin, Sharples, Hernandez, Jick, Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. *BMJ* 2011;340:d2139.
  - <sup>11</sup> Gronich , Lavi, Rennert. Higher risk of non-fatal venous thromboembolism associated with drospirenone-containing oral contraceptives: a population-based cohort study. *CMAJ* 2011, 183:d10.1503,
  - <sup>12</sup>Shapiro and Dinger: Risk of venous thromboembolism among users of oral contraceptives: a review of two recently published studies *J Fam Plann Reprod Health Care*, vol. 36, n° 1, 2010, 33-38.