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## One-year clinical experience on the thromboembolic safety profile of the first prolonged release combined oral contraceptive containing 2 mg dienogest and 0.02 mg ethinyl-oestradiol

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### ABSTRACT

**Background:** The introduction of a prolonged-release combined oral contraceptive (COC) with 2 mg dienogest (DNG) and 0.02 mg ethinyl-oestradiol (EE) in a 24/4 daily regimen in over 17 countries between 2024 and 2025 has been the result of extensive pharmaceutical research and clinical development. The high level of acceptability of this novel formulation is due to its reliable contraceptive efficacy and cycle control.

**Objective:** To describe the incidence of thromboembolic events with the use of the DNG/EE COC based on more than one year of pharmacovigilance data, providing the first indication regarding its safety profile.

**Methods:** After more than one year of clinical experience and over 50,861 women-years of use, 12 cases of VTE were recorded, resulting in a rate of 2.36 VTE events per 10,000 women-years.

**Conclusions:** The reported incidence of VTE under the use of DNG/EE is low, lower than the rate defined by the EMA of 5–7 cases per 10,000 women-years under the use of a COC with levonorgestrel or the summary of product characteristics specified VTE risk of 8–11 cases per 10,000 women-years for the combination of DNG/EE, hence introducing a new safe contraceptive option, in particular for users wishing the anti-androgen properties of such a formulation. This first preliminary report further confirms the safety of the product, providing reassurance to both healthcare providers and patients.

### SHORT CONDENSATION

Spontaneously reported thromboembolic events (VTE) with the prolonged release 2 mg dienogest/0.02 mg ethinyl-oestradiol combined oral contraceptive via pharmacovigilance. After more than one year of clinical experience and over 50,861 women-years of use, 12 cases of VTE were recorded, resulting in a rate of 2.36 VTE events per 10,000 women-years.

### ARTICLE HISTORY

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### KEYWORDS

Dienogest; ethinylestradiol; venous thromboembolic risk; oral contraception; pharmacovigilance data

## Introduction

A first-in-class low-dose prolonged-release combined oral contraceptive (COC) containing 2 mg dienogest (DNG) and 0.02 mg ethinyl-oestradiol (EE) (DNG/EE) has been developed to reduce hormonal plasma fluctuations in comparison with immediate-release formulations (with maximal concentration [C<sub>max</sub>] occurring after 1.5 h) and to delay the time to maximal concentration [T<sub>max</sub>] by a few hours to achieve a globally similar total exposure with reduced peak intensity [1–3].

The pooled efficacy analysis of the prolonged-release DNG/EE formulation has shown a reliable contraceptive efficacy.

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There were only two on-drug pregnancies (both reported in women < 35 years old), which led to a pearl index (PI) for women < 35 years old of 0.2 (95% CI = 0.03, 0.77) [1] for 12,126 exposure cycles (primary endpoint).

On the other hand, to date, no precise data exists regarding the thrombotic risk associated with this specific DNG/EE formulation, other than those derived from the traditional combination of EE 0.03 mg and 2 mg of DNG [4]. For this reason, we considered it useful to report preliminary pharmacovigilance data regarding the number of commercialised cycles of this new COC.

## Material and methods

Although the number of women who were treated with the COC containing DNG/EE during the time of clinical trials was considerable, since the incidence of VTE is low in the target population of women of reproductive age, post-marketing experience provides relevant information on the VTE risk in the population exposed to the drug.

Therefore, a patient exposure calculation for the DNG/EE COC for the years 2024 and 2025 is presented.

The calculation is based on the sales data, and the Defined Daily Dose (DDD) has been used as the best estimate of patients' exposure.

For the 24-tablet cycle package, as there is no DDD defined by the WHO, the Marketing Authorisation Holder has used an estimated DDD of 0.85.

The Estimated Patient Exposure per year was estimated considering that each woman receives an average of thirteen (13) cycles of treatment in one year. Patient-years exposure (PYE) = Total number of cycles sold x 0.85/13.

The DNG/EE COC has been commercialised in 12 European and 4 Latin American countries.

The cumulative number of blisters sold in these countries up to 30 September 2025, is 777,873. The cumulated number of patient-years exposed to the active DNG/EE COC was  $(777,873 \times 0.85) / 13 = 50,861$  patient-years.

## Results

The search was intended to identify cases related to VTE in the 50,861 patient-years of DNG/EE COC use. It was performed using the safety database and the Standardised MedDRA Queries (SMQ) for embolic and thrombotic events. This research identified 12 cases of VTEs, including deep vein thrombosis, and pulmonary embolism. The cut-off date was 30 September 2025.

The cumulative case reporting incidence of VTE in women during their exposure to the DNG/EE COC is  $12 / 50,861$  patient-years = 2.36 per 10,000 patient-years. [Table 1](#) depicts the data.

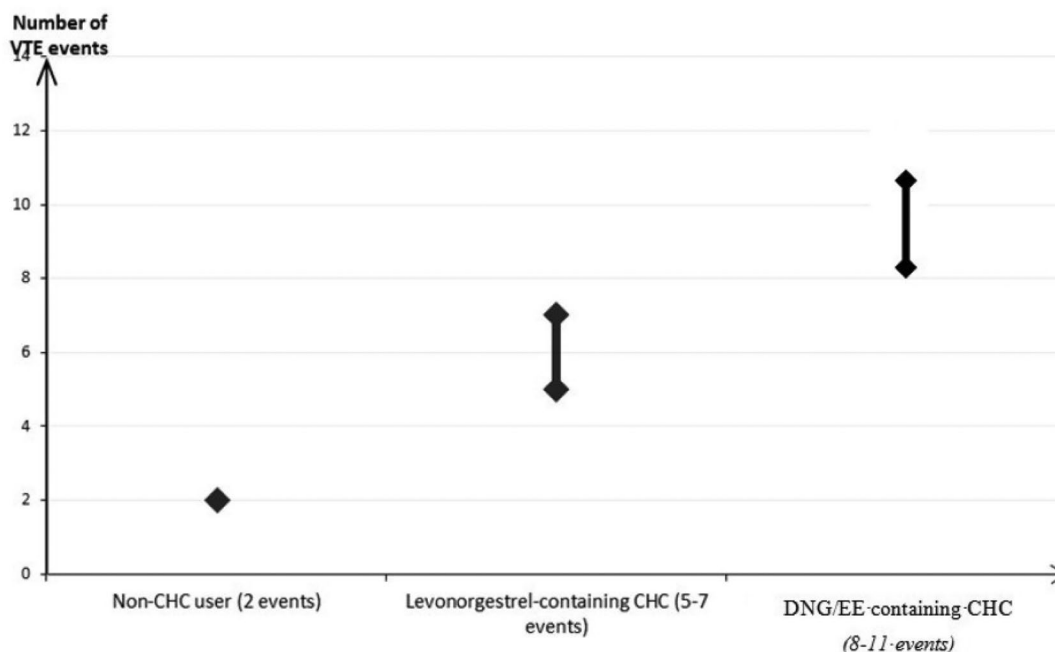
## Discussion

### Findings and interpretation

With an incidence of 2.36 VTE cases per 10,000 women-years in a population of 50,861 women-years (=patient exposure years), these findings represent the first post-marketing evidence regarding the safety of this prolonged-release DNG/EE COC.

**Table 1.** Number of VTE cases under the use of a combined oral contraceptive containing 2 mg dienogest and 0.02 mg ethinyl-oestradiol.

Period	Nr. of VTE cases	Patient exposure years	Reporting
	Cases	PYE	Ratio
Up to 15. March 2025	3	8,472	3.54 per 10,000 Women- years
Up to 30. September 2025	12	50,861	2.36 per 10,000 Women- years



**Figure 1.** Expected VTE risk of a combined oral contraceptive containing 2 mg dienogest and 0.02 mg ethinyl-oestradiol according to the summary of product characteristics (SmPC) of the formulation [1].

### **Results in the context of what is known and clinical implications**

According to the European Medicines Agency (EMA), the estimated incidence of VTE among non-pregnant, non-users of COC is approximately 2 cases per 10,000 women-years, independent of age or other risk factors. For users of COC, EMA cites an incidence of 5–7 cases per 10,000 women-years for preparations containing levonorgestrel, norethisterone, or norgestimate, and 8–11 cases per 10,000 women-years for those containing DNG (see Figure 1) [5].

### **Research implications**

It is noteworthy to note that all different oestrogens on the market (EE, oestradiol, and its valerate and estetrol) exert their activity by coupling to the oestrogen receptors alpha and beta, and that, to date, it has not been possible in epidemiological analyses to demonstrate that one of the oestrogens is safer than the other [6].

The herein reported VTE rate is in the range of that found during natural oestradiol-based COCs in post-marketing trials with similar patient-years exposure [7]. It is still to be understood if the prolonged release of EE can specifically impact the coagulation system and thrombotic risk, but it seems no different from the traditional release [8]: it is therefore relevant to elucidate this VTE risk in real-life experiences.

### **Strengths and limitations**

Over 50,000 women-years of exposure provides meaningful first post-marketing evidence.

As a limitation, the VTE case identification relied on spontaneous reporting and pharmacovigilance data, which may be subject to underreporting, misclassification, and variable diagnostic confirmation. The risk of VTE is known to peak during the first 3–6 months after initiation or reinitiation of a COC or following a switch from another formulation. Most DNG/EE users during this period were incident users, thereby concentrating on risk in the early months of exposure. As cumulative exposure increases and more users transition to the prevalent phase, the observed VTE incidence is expected to stabilise or decline [9]. Newly launched contraceptive products frequently experience increased spontaneous reporting due to increased prescriber and patient vigilance. This phenomenon can inflate apparent incidence

during early post-marketing phases. Historical examples include other hormonal contraceptives, which showed early post-marketing spikes in VTE reporting that decreased with broader use and prescriber confidence [10].

## Conclusions

This analysis of the COC containing dienogest and 0.02 mg ethinylestradiol provides initial real-life data on VTE risk, with an incidence of 2.36 cases per 10,000 women-years across 50,861 women-years of exposure. While this estimate appears lower than the ranges reported for other COCs, interpretation should be cautious due to the limited exposure time and the intrinsic limitations of pharmacovigilance reporting. Nevertheless, the number of patient years is sufficient to generate a valid assessment of the risk of VTE of this 2 mg DNG/0.02 mg EE COC after the first year of market authorisation. Continued surveillance with larger populations and longer follow-up will be essential to define the long-term VTE risk of this formulation more precisely and to place it in context with existing contraceptive options.

## Author contributions

CRedit: **Giovanni Grandi**: Data curation, Formal analysis; **Inka Wiegatz**: Data curation, Validation, Writing – review & editing; **Enrico Colli**: Investigation, Resources, Supervision, Validation; **Alicyoy Angulo**: Conceptualization, Investigation, Validation; **Pedro-Antonio Regidor**: Conceptualization, Writing – original draft, Writing – review & editing.

## Disclosure statement

Alejandro Munoz, Enrico Colli, Alicyoy Angulo and Pedro-Antonio Regidor are employees of Exeltis Pharmaceutical member of Insud Pharma. Giovanni Grandi received research funding, consultancy and/or lecture fees from Bayer, Exeltis, Organon, Gedeon Richter, Theramex, Italfarmaco, Farmitalia and Opocrin. Inka Wiegatz received research funding, consultancy and/or lecture fees from Bayer, Exeltis, Gedeon Richter, Jenapharm, Pfizer Pharma GmbH, Theramex.

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## Data availability statement

The data that support the findings of this study are available from the corresponding author, [PAR], upon reasonable request.

## References

- [1] Kelzy. Dienogest/ethinyl estradiol 2 mg/0.02 mg prolonged-release tablets. Summary of Product characteristics; 2024. Available from: [https://docetp.mpa.se/IMF/Dienogest\\_ethinylestradiol%20exeltis%20prolonged-release%20tablets%20eNG%20smPc\\_09001bee83c7d1de.pdf](https://docetp.mpa.se/IMF/Dienogest_ethinylestradiol%20exeltis%20prolonged-release%20tablets%20eNG%20smPc_09001bee83c7d1de.pdf).
- [2] Biskupska-Bodova K, Sójka-Kupny J, Nyirády T, et al. Randomized double-blind trial to determine the bleeding profile of the prolonged-release contraceptive dienogest 2 mg/ethinylestradiol 0.02 mg versus an immediate-release formulation of drospirenone 3 mg/ethinylestradiol 0.02 mg. *Eur J Contracept Reprod Health Care*. 2025;30(1):3–12. doi: [10.1080/13625187.2024.2398433](https://doi.org/10.1080/13625187.2024.2398433).
- [3] Grandi G. Hormonal prolonged-release in oral contraception: how far are we from vaginal pharmacokinetics? *Eur J Contracept Reprod Health Care*. 2025;30(3):123–124. doi: [10.1080/13625187.2025.2485217](https://doi.org/10.1080/13625187.2025.2485217).
- [4] Schink T, Princk C, Braitmaier M, et al. Use of combined oral contraceptives and risk of venous thromboembolism in young women: a nested case-control analysis using German claims data. *BJOG*. 2022;129(13):2107–2116. doi: [10.1111/1471-0528.17268](https://doi.org/10.1111/1471-0528.17268).
- [5] <https://www.ema.europa.eu/en/medicines/human/referrals/combined-hormonal-contraceptives>.
- [6] <https://www.fda.gov/media/186470/download?attachment>.

- [7] Grandi G, Facchinetti F, Bitzer J. Confirmation of the safety of combined oral contraceptives containing oestradiol on the risk of venous thromboembolism. *Eur J Contracept Reprod Health Care*. 2022;27(2):83–84. doi: [10.1080/13625187.2022.2029397](https://doi.org/10.1080/13625187.2022.2029397).
- [8] Regidor PA, Angulo A, Colli E. Effect over coagulation and fibrinolysis parameters of a prolonged release 24+4 daily use regime contraceptive formulation containing 2mg dienogest/0.02mg ethinylestradiol. *Gynecol Endocrinol*. 2025;41(1):2458708. doi: [10.1080/09513590.2025.2458708](https://doi.org/10.1080/09513590.2025.2458708).
- [9] Practice Committee of the American Society for Reproductive Medicine. Electronic address: [ASRM@asrm.org](mailto:ASRM@asrm.org); Practice Committee of the American Society for Reproductive Medicine. Combined hormonal contraception and the risk of venous thromboembolism: a guideline. *Fertil Steril*. 2017;107(1):43–51. Epub 2016 October 25. doi: [10.1016/j.fertnstert.2016.09.027](https://doi.org/10.1016/j.fertnstert.2016.09.027).
- [10] Hoffman KB, Demakas AR, Dimbil M, et al. Stimulated reporting: the impact of US food and drug administration-issued alerts on the adverse event reporting system (FAERS). *Drug Saf*. 2014;37(11):971–980. doi: [10.1007/s40264-014-0225-0](https://doi.org/10.1007/s40264-014-0225-0).