boletim de FARMACO VIGILÂNCIA

VOLUME 23
NUMBER 5
MAY 2019

Dienogest/ethinylestradiol: Slightly higher relative risk of venous thromboembolism

Quick Read

The benefits from the use of combined hormonal contraceptives (CHCs) remain higher than the attending risk of serious collateral effects. However, prescription decisions should take the risk profile of each individual woman into account. Users of any CHC have an associated increase in the risk of venous thromboembolism (VTE) when compared with non-users, especially during the first year of exposure. Risk varies slightly among contraceptives but those with the lowest risk contain levonorgestrel, norethisterone or norgestimate for a progestagen. Pregnancy and puerperium are meanwhile associated with the greatest risk.

The combination of ethynilestradiol with the progestagen dienogest is indicated in oral contraception. The underlying mechanism of action results from the interaction of various factors, namely inhibition of ovulation and changes in cervical mucus. Whenever oral contraceptives are prescribed, each individual woman's risk factors need to be borne in mind and especially so the risk of venous thromboembolism (VTE – deep venous thrombosis, pulmonary embolism).

The information concerning Valette® (a CHC marketed in Portugal) has recently been reviewed at European level in what regards the risk of VTE in women taking dienogest/ethynilestradiol (DNG/EE) versus users of other CHCs containing levonorgestrel/ethynilestradiol (LNG/EE).

The assessment looked at a **metaanalysis** of four l**arge, controlled, prospective observational studies** following a series of cohorts: the **LASS** (*Long-term active surveillance study for oral contraceptives*), **INAS-OC** (*International active surveillance study of women taking oral contraceptives*), **TASC** (*Transatlantic active surveillance on cardiovascular safety of Nuvaring (etonogestrel/ethinylestradiol vaginal ring*) and **INAS-SCORE** (***International active surveillance study – safety of contraceptives: role of estrogens***) studies.

The assessment as a whole included data from 228,122 users of hormonal contraceptives. The European study subjects had used DNG/EE and LNG/EE (products with only 30 µg EE) for 38,708 woman-years and 45,359 woman-years, respectively. The metaanalysis turned out an adjusted odds ratio of 1.57 (95% CI: 1.07–2.30) for the risk of VTE with dienogest + ethynilestradiol as compared to levonorgestrel + ethynilestradiol. It was thus concluded that CHCs containing DNG/EE are associated with a comparatively slightly higher risk of VTE.

Based on these statistical results, the annual risk of women using dienogest + ethynilestradiol is estimated to be of 8 to 11 cases of VTE per 10,000 women. By comparison, the annual number of cases of VTE in women using CHCs containing levonorgestrel, norethisterone or norgestimate is 5 to 7 per 10,000 women. The baseline risk of VTE in non-users is of two cases per 10,000 women (Table 1, overleaf).

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Design and production: Letras & Sinais, Comunicação e Imagem, Lda.
ISSN: 0873-7118

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Progestagen in CHC (in combination with ethynilestradiol, except when stated otherwise)	**Relative risk** In comparison with **levonorgestrel**	**Estimated incidence** (per 10,000 women per year of use)
Non-pregnant non-user	–	2
Levonorgestrel	*reference*	*5 – 7*
Norgestimate / Norethisterone	1.0	*5 – 7*
Dienogest	**1.6**	**8 – 11**
Gestodene / Desogestrel / Drospirenone	1.5 – 2.0	9 – 12
Etonorgestrel / Norelgestromin	1.0 – 2.0	6 – 12
Chlormadinone / Nomegestrol acetate (with estradiol)	To be confirmed	To be confirmed

Table 1. Risk of VTE with combined hormonal contraceptives (new data in bold).

It can therefore be seen that the risk of VTE varies slightly among contraceptives, the ones containing the **progestagens levonorgestrel, norethisterone and norgestimate** showing the smallest risk.

The use of any CHC meanwhile, increases the risk of VTE in comparison to non-users. Risk is highest in the **first year of use** of any CHC **or after resumption** following a pause of four or more weeks.

When compared to **pregnancy and the post-partum period** however, the risk of VTE associated with the use of **any CHC** is **lower**.

The risk of VTE is higher in the presence of **intrinsic risk factors** and can change with time. Any woman with **suggestive signs and symptoms** should be asked about the uptake of medicines, especially CHCs, so that a diagnosis can be made as early as possible. A significant number of cases of thromboembolism is not preceded by obvious clinical manifestations.

The **benefits from the use of CHCs outweigh the risk of serious side effects but the decision to prescribe should take the woman's actual risk factors into account**. Prescribers should make women aware of the signs and symptoms of thromboembolism and periodically assess their individual risk factors.

The Summary of the Product's Characteristics (SmPC) and the Patient Information Leaflet of Valette® (dienogest/ethynilestradiol) will be updated accordingly.

Maria Fernanda Marques

Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Comunication Online publication date
Agomelatine Agomelatina ratiopharm Agomelatina Teva	**Physicians:** psychiatry and neurology	Prescriber guide on liver monitoring and interaction with potent CYP1A2 inhibitors
	Patients	Information card 07-05-2019
Apixaban Eliquis	**Physicians:** cardiology, neurology, internal medicine, general/family medicine, haematology/ immunohaemotherapy, anaesthesiology, orthopaedics, vascular surgery and gastroenterology; clinical directors **Pharmacists:** : hospital pharmaceutical service directors	Prescriber's guide 17-05-2019
Asfotase alfa Strensiq	**Patients**	Self-injection guide
	Parents and adults in charge of children	Injection guide 24-05-2019
Emtricitabine + Tenofovir Emtricitabina + Tenofovir Teva	**Physicians:** infectious diseases and internal medicine	Prescriber's guide (for PrEP) Prescriber's checklist (for PrEP
	Patients (at-risk individuals)	Patient guide (for PrEP) Patient reminder card (for PrEP) 21-05-2019
Levonorgestrel Levosert	**Patients** (educational material to be handed out by physicians skilled in uterine device insertion: gynaecology/obstetrics and general/family medicine)	Patient card 02-05-2019
Paracetamol + Thiocolchicoside Descontran	**Physicians:** general/family medicine, orthopaedics, rheumatology, rehabilitation medicine, gynaecology, and internal medicine **Pharmacists**	Healthcare professional's guide
	Patients	Information card 20-05-2019
Sebelipase alfa Kanuma	**Physicians:** paediatrics, gastroenterology, internal medicine, endocrinology **Nurses:** who administer this medicine	Healthcare professional's guide 27-05-2019

Compiled by Magda Pedro

Communications to Healthcare Professionals published on the Infarmed website

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INN Medicinal product	Target	Comunication Online publication date
Anticoagulants, direct: **Apixaban** Eliquis **Dabigatran** Pradaxa **Edoxaban** Lixiana, Roteas **Rivaroxaban** Xarelto	**Physicians:** general/family medicine, internal medicine, cardiology, haematology, immunohaemotherapy, angiology, vascular surgery, orthopaedics, and rheumatology **Pharmacists**	Not recommended in patients with antiphospholipid antibody syndrome due to possible increase in the risk of recurrent thrombotic events 20-05-2019
Domperidone Cinet Domperidona Aurovitas, Azevedos, Baldacci, Generis, GP, Labesfal, Mylan, Ratiopharm, ToLife Motilium Remotil	**Physicians:** general/family medicine, paediatrics and gastroenterology; gynaecology/obstetrics, neurology, oncology, haematology, and emergency department directors **Pharmacists:** community and hospital	Removal of the paediatric posology and reinforcement of information on approved indication and contraindications in relation with serious adverse cardiac reactions 17-05-2019
Lapatinib Tyverb	**Physicians:** oncologists, gynaecologists and internists (who follow breast cancer patients)	Important update of the Summary of the Product's Characteristics (SmPC) resulting from the detection of errors in an efficacy study 17-05-2019
Olaratumab Lartruvo	**Physicians:** oncologists **Nurses:** day care hospital nursing directors **Pharmacists:** pharmaceutical service directors	Revocation in the EU due to lack of efficacy 06-05-2019
Tofacitinib Xeljanz	**Physicians:** rheumatologists, internists and dermatologists who undertake rheumatoid arthritis and psoriatic arthritis clinics, gastroenterologists	Restriction to the use of the 10-mg twice daily dose in patients at high risk of pulmonary embolism 28-05-2019

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E-book chapter 7.1.
Adverse reaction mechanisms and their clinical relevance (Carlos Fontes Ribeiro)

Most adverse reactions to medicines are due to absolutely or relatively elevated doses or to the drug's own mechanism of action (type A reactions) and can often be prevented. Unexpected lack of efficacy (therapeutic failure) can also be viewed as an adverse reaction (type F). Other pathophysiological mechanisms are also possible: immunological or idiosyncratic (type B adverse reactions), repeat or continuous exposure to the product (type C), delayed appearance to do with carcinogenesis or teratogenesis (type D), or reactions resulting from withdrawal/eviction of the drug (type E).

Variations in drug blood concentrations can be due to pharmacokinetic changes associated with genetic polymorphisms, diseases, interactions or physiological conditions or changes, such as ageing. They may also result from absolute or relative overdosing (toxic effects). Pharmacodynamic changes can also be at the origin of adverse reactions - for instance, changes in receptors, in the genes coding them or in their expression (epigenetics), changes in signalling pathways and in ion channels. Differently, a great number of serious and preventable adverse reactions may be ascribed to medication errors.

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