IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

59TH EDITION

Combined Hormonal Contraceptives – Update on Risk of Venous Thromboembolism

The benefits of combined hormonal contraceptives (CHCs) in pregnancy prevention are well established. It has also long been recognised that all CHCs are associated with a small increase in the risk of venous thromboembolism (VTE), compared with no use. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency recently carried out a review of all available evidence on the safety and efficacy of CHCs and confirmed that the balance of benefits and risks for CHCs remains positive in preventing unplanned pregnancies. The outcome of the review also supported the previous understanding that the absolute risk of VTE with CHCs is small, but that the risk differs depending on the type of progestogen they contain, for a given dose of oestrogen.

PRAC Review and Recommendations

The PRAC reviewed the available data on CHCs, in particular in relation to the risk of thromboembolism[1]. This included data from clinical and pharmacoepidemiological studies, published literature, post-marketing experience and responses submitted by the marketing authorisation holders. In addition, meetings with experts were convened, the opinions of which were also considered in the assessment.

Risk of Venous Thromboembolism

Review of the data confirmed that the absolute risk of VTE with all CHCs is small and ranges from 5 to 12 cases of VTE per 10,000 women per year (see table below). The review also confirmed that differences exist between CHCs in their risk of VTE depending on the type of progestogen they contain, with available evidence indicating those CHCs containing levonorgestrel, norethisterone or norgestimate have the lowest risk of VTE. Best estimates of the risk of VTE with a number of ethinylestradiol/progestogen combinations compared with the risk associated with levonorgestrel-containing products are shown in table 1.

Table 1: Risk of VTE with combined hormonal contraceptives

Progestogen in CHC (combined with ethinylestradiol, unless stated)	Relative risk vs Levonorgestrel	Estimated incidence of VTE (per 10,000 women per year of use)
Non-pregnant non-user	—	2
Levonorgestrel	Ref	5-7
Norgestimate / Norethisterone	1.0	5-7
Gestodene / Desogestrel / Drospirenone	1.5-2.0	9-12
Etonorgestrel / Norelgestromin	1.0-2.0	6-12
Chlormadinone / Dienogest / Nomegestrel acetate (Estradiol)	Not yet known*	Not yet known*

* Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products.

In this edition

Compared with pregnancy and the postpartum period, the risk of VTE associated with using CHCs is lower. With all CHCs the risk is greatest in the first year of use, or upon re-starting CHCs after a break of 4 or more weeks. The risk of VTE is also higher in the presence of intrinsic risk factors, these may change over time and so an individual's risk should be re-evaluated periodically.

The PRAC also concluded that the baseline VTE rate is slightly higher than previously thought. These increased rates are likely due to improvements in VTE diagnosis and reporting, as well as an increase in obesity rates over time.

The PRAC recommended that the product information be updated to ensure healthcare professionals and patients can make fully informed decisions about the most suitable choice of contraceptive. The product information [Summaries of Product Characteristics (SmPCs) and Package Leaflets (PLs)] for CHCs will be updated to ensure clear presentation of the information on VTE risk, including risk factors for VTE and contraindications for use of CHCs. In addition, the importance of ensuring that patients are aware of the risk of VTE and its signs and symptoms will be reinforced in the product information. A Direct Healthcare Professional Communication (DHPC) highlighting these updates to product information has been circulated and published on the IMB website (**www.imb.ie**).

Risk of Arterial Thromboembolism

The PRAC also considered the risk of arterial thromboembolism (ATE) and confirmed that the risk remains very low. There is insufficient evidence to suggest a difference in the level of risk between products depending on the type of progestogen.

Classification of Progestogens

The PRAC conclusions presented the updated risk estimates in relation to specific progestogens. The traditional classification of CHCs and progestogens by 'generations' (reflecting when they were developed) is not science-based and has been found to be used inconsistently between institutions and publications. The PRAC review included CHCs containing a low-dose oestrogen and a progestogen (see full list below).

Advice for Healthcare Professionals

- If a woman has been taking a CHC without any problems, there is no reason for her to stop taking it on the basis of this review.
- The decision about which product to use should be taken only after a discussion with the woman that includes the level of VTE risk associated with different products; how her current risk factors influence the risk of VTE and ATE, and exploration of her preferences.
- When prescribing a CHC, careful consideration should be given to:
  - Contraindications for use, which include patients with, or a risk of venous or arterial thromboembolism, such as history of deep vein thrombosis, pulmonary embolism, arterial thrombosis or prodromal condition, known hereditary or acquired predisposition for VTE or ATE, major surgery with prolonged immobilisation, history of migraine with focal neurological symptoms and high risk of venous or arterial thrombosis due to multiple risk factors.
  - The individual woman's current risk factors for VTE (these include smoking, being overweight, increasing age, migraines, family history of VTE and recent birth). A woman's individual risk factors for VTE should also be assessed at regular intervals during treatment as the risk changes over time.
- Patients should be made aware of the risk of VTE, counselled on the signs and symptoms and instructed to seek medical advice immediately if they develop any of these signs or symptoms.

- Prescribers are reminded that a significant proportion of cases of thromboembolism are not preceded by any obvious signs or symptoms.

- Women should be advised not to smoke if they wish to use a CHC. Women over 35 years of age who continue to smoke should be strongly advised to use a different method of contraception.

Key Messages

- **The benefits associated with using a CHC to prevent pregnancy far outweigh the risk of serious side effects in most women.**
- **The absolute risk of VTE with all CHCs is small and current data indicate this is lowest with CHCs which contain levonorgestrel, norgestimate and norethisterone.**
- **When choosing a suitable CHC, prescribers should consider the contraindications for use of CHCs, a patient's individual risk factors for VTE and the difference in VTE risk depending on the type of progestogen a product contains.**
- **Patients should be made aware of the signs and symptoms of VTE and instructed to seek medical attention immediately should these symptoms develop.**

The review included all contraceptives containing low dose oestrogen and the progestogens listed below. The brand names listed are all authorised in Ireland, some of which are not currently marketed.

Chlormadinone (not authorised in Ireland)

Desogestrel (Gracial, Leticia, Marviol, Mercilon, Vivides)

Dienogest (Qlaira)

Drospirenone (Carmen, Carmenelle, Dretine, Dretinelle, Enador, Flexyess, Freedo, Freedonel, Liofora, Palandra, Svelta, Veyann, Yasmin, Yasminelle, Yaz)

Etonogestrel (Circlet, Nuvaring)

Gestodene (Estelle, Harmonet, Minesse, Minulet)

Levonorgestrel (Leonore, Logynon, Microlite, Ovranette, Rigevidon)

Nomegestrol (Ioa, Zoely)

Norelgestromin (Evra)

Norethisterone (not authorised in Ireland as part of a combined hormonal contraceptive)

Norgestimate (Cilest)

1. Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks – CHMP endorses PRAC recommendation. European Medicines Agency press release 22nd November 2013. www.ema.europa.eu

Electronic Distribution of the IMB Drug Safety Newsletter (DSN)

Welcome to the 59th Edition of the IMB's Drug Safety Newsletter (DSN) and the first fully electronic version of this publication. Changes to the arrangements for publication and distribution were highlighted in several editions of the DSN during 2013, inviting readers to register with the IMB to receive alerts when new editions of the DSN are published on the IMB website. The IMB is also continuing to work with the relevant healthcare professional organisations to facilitate distribution of the DSN via their networks, as electronic distribution is now the main method of circulation of the DSN.

The electronic version of the DSN is in PDF format, thus allowing you to save the newsletter and/or print specific pages. The online version also contains hyperlinks to product information and other documents on the IMB and European Medicines Agency (EMA) websites.

Direct Healthcare Professional Communications published on the IMB website since the last Drug Safety Newsletter

Product	Safety Issue
Zofran (ondansetron)	Communication on ondansetron and dose-dependent QT interval prolongation-updated information on posology for intravenous use.
Abraxane (paclitaxel)	Visible strands in the intravenous infusion bag.
Increlex (mecasermin)	Stock shortage has been resolved.
Erbitux (cetuximab)	Communication on the importance of establishing wild-type RAS status before treatment with Erbitux.
Arzerra (ofatumumab)	Communication as a reminder that all patients should be screened for hepatitis B virus before treatment.
Flixonase Allergy Relief (fluticasone propionate)	Restriction of use to adults (aged over 18 years) only due to growth velocity reductions concerns in children.
Temodal (temozolomide)	Communciation on severe liver toxicity associated with Temodal.
Xeloda (capecitabine) (Xeloda).	Communication on severe skin reactions associated with Capecitabine
Inclusig (ponatinib)	Updated advice on the risk of vascular occlusive events.
Fastum Gel (ketoprofen)	Communication on risk minimisation measures for ketoprofen-containing topical formulations.

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