21 November 2013
EMA/739865/2013

Assessment report

Combined hormonal contraceptives containing medicinal products

Procedure under Article 31 of Directive 2001/83/EC

INN: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate

Procedure number: EMEA/H/A-31/1356

Zoely EMEA/H/A-31/1356/C/1213/0010
Ioa EMEA/H/A-31/1356/C/2068/0007
Evra EMEA/H/A-31/1356/C/410/0031

Note

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
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1. Background information on the procedure

On 5 February 2013, further to evaluation of data resulting from pharmacovigilance data, France informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC, of their consideration that the benefit risk balance of combined hormonal contraceptives had become unfavourable in the currently authorised indication due to the increased risk of thromboembolism (TE) and therefore it was in the interest of the Union to refer the matter to the PRAC. The PRAC was requested to give a recommendation on whether the indication of medicinal products containing chlormadinone (CMA), desogestrel (DSG), dienogest (DNG), drospirenone (DRSP), etonogestrel (ENG), gestodene (GSD), norelgestromin (NGMN), norgestimate (NGM) or nomegestrol (NOMAC) should be restricted and/or any other regulatory measures taken.

2. Scientific discussion

Contraceptive pills were first introduced in the early 1950's. The first combined contraceptive pill contained the progestogen norethinodrel and high doses of oestrogens (mestranol). Ethinylestradiol (EE)-containing CHCs were introduced in the 1960's. They also contained a high dose of oestrogen (up to 150 µg).

Studies soon showed that the use of these preparations was associated with an increased risk of venous thromboembolism and that this was dependent on the dose of the oestrogen component. Subsequent studies showed that the risk was much reduced by lowering the dose of oestrogen and this resulted in the introduction of newer preparations containing <50 µg oestrogen. However, with the lower doses of oestrogen came the realisation that the characteristics of the progestogen may also have an influence on the risk of thromboembolism. The early progestogens were all derived from testosterone and concerns over their possible risk of thromboembolism resulted in the design of a newer set of progestogens. As a result of their phased introduction to the market, the different types of CHCs have been categorised into 'generations'. The method of categorisation is not standardised and is based variously on the progestagen or on the time of introduction to the market. In practice this has resulted in studies on thromboembolism, with e.g. products being categorised as a 'third generation' pill, a 'fourth generation' pill' and as a 'second generation' pill, which makes the interpretation of results for the individual progestogens challenging.

Nine progestogens fall within the scope of this referral (chlormadinone (CMA), desogestrel (DSG), dienogest (DNG), drospirenone (DRSP), etonogestrel (ENG), gestodene (GSD), norelgestromin (NGMN), norgestimate (NGM) or nomegestrol (NOMAC)). These are combined with varying doses of ethinylestradiol (EE) or with estradiol (E2). The combined hormonal contraceptives include oral tablets known as combined oral contraceptives (COCs), as well as one transdermal patch and vaginal inserts (rings).

2.1. Clinical aspects

2.1.1. Clinical safety

The adverse events common to all CHCs are well-documented and include breast tenderness, nausea, headache, weight gain and acne. These are listed in the relevant product information of the different products.

The occurrence of these mild side effects varies according to the preparation. They affect the quality of life of the woman and are important predictors of compliance. The availability of a range of contraceptive options is therefore important because certain preparations will be unacceptable to some women. Tolerability issues are most common in the first year of use and, evidence suggests that the CHC is not always substituted immediately for an equally effective contraceptive, resulting in unintended pregnancy (*Rosenberg*, 1995).

As a class, the combined hormonal contraceptives have also been associated with a number of more rare but serious adverse effects, such as hepatobiliary disorder, exacerbation of hereditary angioedema, pancreatitis, breast cancer, increase in blood pressure and thromboembolism. These are listed in the product information.

Although all these effects play an important part in the overall balance of benefits and risks of CHCs the greatest risk for a young healthy woman during current use is that of thromboembolism. This referral and subsequently this assessment report will focus on the assessment of the risk of thromboembolism. Due to the very large availability of data only relevant data will be presented here while all available data have been assessed.

2.1.1.1. Thromboembolism

In the context of this review on the thromboembolic risk associated with CHCs, the MAHs were requested to submit all data relevant to VTE and ATE. Most MAHs submitted detailed summaries of their clinical studies but after review, it was concluded that in view of the low frequency of VTE, clinical studies were not sufficiently powered to evaluate this effect.

Post-marketing data have also been provided in the context of this review. However, these are subject to a diversity of influences on levels of reporting, including year of introduction of product to market, media interest, litigation, among others and it is therefore difficult to use these data to compare the risk of adverse reactions between products.

In view of the limitations of the clinical studies, this report focuses on the pharmacoepidemiology studies on CHCs in order to have the estimated relevant risk.

A. Effect of progestogen on risk of VTE

The pharmacoepidemiological data of the different CHCs are presented below.

Dienogest (DNG)

Dienogest is derived from 19-nortestosterone (a C-19 progestogen) and has anti-androgenic action (estimated to be about one third that of cyproterone acetate). It also has a strong *in vivo* progestogenic effect and no significant androgenic, glucocorticoid or mineralocorticoid activity. There are two groups of dienogest-containing products, a combination of dienogest with ethinylestradiol as well as a combination of dienogest with estradiol.

i. Dienogest/ethinylestradiol

Two case-control studies evaluated the risk of VTE with DNG/EE were evaluated. Both were conducted by the German ZEG centre (*Heinemann et al*., 2001; *Dinger et al*., 2010). In addition, a post-hoc analysis of an European Active Surveillance Study (EURAS) was conducted at the request of the regulatory authorities.

Heinemann case-control study (2001)

The objective of the Heinemann case-control study (2001) was to compare the risk of VTE in users of DNG/EE with the risk in users of low-dose second generation COCs that contained any progestogen other than desogestrel (DSG) or gestodene (GSD) aged 15-49 years between 1994 and 1999. This was a community-based case control study that recruited all suspected cases of VTE from practice/hospital records of 21 practices, diagnostic centres and hospitals in Germany. Diagnoses were verified based on clinical findings, lab tests, imaging procedures and subsequent specific therapy following a predefined algorithm. VTE was defined as "idiopathic" when neither a history of VTE nor a causal factor for VTE (defined as pregnancy, delivery, surgery, trauma, and/or immobilisation) was found in the six weeks prior to the event. Each practice case was matched with community-based controls according to year of birth and area of residence. Controls for the hospital cases came from the same hospital matched for age and date of hospitalisation.

In users of DNG-COC or 'second generation' COCs, 226 cases and 1109 controls were identified. In non-users, 313 cases and 2688 controls were identified.

Table 1: Risk estimates for VTE associated with DNG/EE or use of second generation COCs

Comparison	Point Estimate $OR_{adjusted*}$	95% Confidence Interval
Idiopathic cases		
DNG/EE vs. No use	2.2	1.2 – 4.0
"2nd generation" COCs vs. No use	2.6	2.0 – 3.4
DNG/EE vs. "2nd generation" COCs	0.9	0.5 – 1.7
All cases (idiopathic and non-idiopathic)		
DNG/EE vs. No use	1.3	0.8 – 2.3
"2nd generation" COCs vs. No use	2.0	1.7 – 2.5
DNG/EE vs. "2nd generation" COCs	0.7	0.4 – 1.3

DNG = dienogest, EE ethinylestradiol, COC = combination oral contraceptive, OR = odds ratio, "2nd generation COCs: <50µg EE, all progestins except desogestrel, gestodene, and DNG.
* adjusted for age (5 years), parity, ever use of OC, body mass index (4 categories)

The study results showed no indication of a higher risk of VTE with DNG/EE compared with second generation COCs.

The *German case-control study (*Dinger *et al., 2010)* was a retrospective case-control study in Germany commissioned primarily to investigate whether the VTE risk with DNG/EE was higher than the risk with COCs containing ≤30µg EE, especially those containing LNG. Eligible cases were women, aged 15–49 years, with a clinical diagnosis of VTE (confirmed by imaging procedures or clinical examination plus a positive result from a less specific diagnostic test and/or specific anticoagulatory treatment) between January 2002 and February 2008. Each case was matched with four community-based controls according to year of birth and area of residence.

A questionnaire for women collected data on age, past and current use of hormonal contraception, body weight and height, smoking habits, personal and family history of VTE, varicose veins, recent

immobilisation, pregnancy, surgery and accidents, and genetic risk factors as well as chronic diseases, concomitant medication, socioeconomic and lifestyle indicators.

A total of 680 confirmed VTE cases and 2720 matched controls were included in the study. A total of 35 cases and 106 controls had used a COC containing DNG/EE, and 60 cases and 197 controls had used a LNG/COC.

Current use of any COC was associated with about a two-fold increase in risk of VTE compared with no use, which increased after adjustment for nine potential confounders (adj OR 2.4; 1.8-3.2). Use of DNG/EE was associated with a similar VTE risk compared with use of other low-dose COCs, including low-dose COCs containing LNG. Adjustment for potential confounders resulted in slight or no changes in the risk estimates. No difference in relative risk was observed when idiopathic VTE only was considered (adj OR 1.1; 0.5–2.1).

Table 2: Risk estimates for VTE with DNG/EE versus other low-dose COCs and low dose LNG/EE

Comparison	Point Estimate	95% Confidence Interval
1) DNG/EE vs. Other LD[a] COCs		
OR_{crude}	0.87	0.57 – 1.32
$OR_{adj.\ 9*}$	0.88	0.55 – 1.39
$OR_{adj.\ 4**}$	0.89	0.57 – 1.38
2) DNG/EE vs. LD[a] LNG		
OR_{crude}	1.08	0.67 – 1.75
$OR_{adj.\ 9*}$	1.02	0.60 – 1.75
$OR_{adj.\ 4**}$	1.12	0.67 – 1.87

DNG = dienogest EE ethinylestradiol, COC = combination oral contraceptive, LNG = levonorgestrel, OR = odds ratio
[a] low dose (< 30mcg EE)
* adjusted for 9 covariates: personal history of VTE, family history of VTE, body mass index, duration of COC use, parity, educational level, chronic disease, concomitant medication, and smoking
** adjusted for 4 covariates: personal history of VTE, family history of VTE, chronic disease, and parity

The study did not find any evidence of increased VTE risk among users of DNG/EE compared with other low-dose COC users or of low-dose LNG/EE-COC.

This study represented an updated version of the Heinemann case-control study, covering the period 2002 –2008. It included more than twice the number of cases exposed to DNG/EE. Given the statistical power of the study, the authors concluded that the analyses confirmed that a 2-fold increased risk of VTE in users of DNG/EE compared with other low dose COCs or with low-dose LNG/EE could be excluded. Nevertheless, with an upper 95% confidence interval of 1.8, this study could not exclude an increase in risk of equivalent magnitude to that with contraceptives containing desogestrel, gestodene or drospirenone.

Post hoc analysis of the *European Active Surveillance (EURAS) OC study (*Dinger *et al.,* 2007*)*

The EURAS study was not designed nor powered to assess the specific risk of COCs containing DNG, but the study investigator was asked to conduct a *post hoc* analysis.

A total of 12,206 women-years of exposure to DNG-containing COCs with 30 µg EE were included in the final study analysis. These data were compared with 16,649 women-years of exposure to LNG-containing COC with 30 µg EE. A total of 16 women exposed to DNG had VTEs (including 2 cases of PE), while a total of 17 women exposed to LNG had VTEs (including 4 cases of PE).

Based on this *post hoc* analysis, the incidence rate ratio for VTE in DNG-COC users compared with LNG-COC users was 1.28 (95% CI 0.62 – 2.72), the incidence rate ratio for PEs was 0.68 (95% CI 0.06 – 4.78) and the overall thromboembolic risk estimate for DVT and PE was 1.12 (95% CI 0.56-2.22). This suggests that DNG-COC users do not have a higher thromboembolic risk compared with LNG-COC users.

With respect to the risk of ATE, a total of 25 ATEs were observed: 11 acute myocardial infarctions (MIs), 13 strokes and one complete thrombosis of the hepatic artery proper. Transient ischemic attacks (TIAs) were not included among the strokes. Two women exposed to DNG had ATEs compared with five women exposed to LNG, giving an incidence rate ratio of 0.55 (95% CI 0.05 – 3.35) for the comparison.

The EURAS study is considered to be methodologically sound. However, as this was a *post-hoc* analysis caution has been expressed with regards to the analyses.

Substantial clinical safety information has been collected from several company-sponsored post-marketing studies conducted between 1995 and 2007. Two of these contributed data from approximately 27,000 women with 12,000 women-years of exposure, and did not provide evidence of specific or unexpected new risks (Zimmermann *et al.,* 1999 and 2000). Three cases of thromboembolism were reported in the first study and in the second study, two women suspected to have a superficial thrombophlebitis discontinued the product because of leg pain. Other post-marketing studies included a small number of patients and did not report any cases of venous and arterial thromboembolism. However, these studies were designed to assess efficacy and tolerability in the post-marketing environment and not to assess the risk of thromboembolism.

ii. Dienogest/estradiol

No final results from pharmaco-epidemiological studies on the effects of estradiol/ estradiol valerate containing COCs are yet available.

The INAS-SCORE is a post-authorization safety study which was requested by the EMA. It started in 25,000 women in the EU (Austria, France, Germany, Italy, Poland, Sweden and UK; started September 2009) and 25,000 women in the USA (started October 2010) and is currently ongoing. This prospective, controlled, non-interventional, active surveillance, new user cohort study was designed to assess the risks of short- and long-term use of DNG/E2 and established COCs in a population representative for actual users of the individual preparations. The primary outcomes of interest are cardiovascular events, in particular the incidence of VTE, ATE and acute myocardial infarction (AMI). The final report is expected for Q4 2014. Participants are new users (including first-ever COC users [starters], women who change their COC without a break or with a break of less than 4 weeks [switchers], or women who restart COC use after an intake break of at least 4 weeks [re-starters] and contribute follow-up information for up to five years after study entry.

All self-reported 'clinical outcomes of interest' are validated by health care professionals. All analyses adjust for confounding, using multivariate techniques such as Cox regression models.

As of 31 October 2012, 49,385 study participants have been included of which 10,169 were DNG/E2 users (20.6% of total study population) and 39,216 were users of 'Other COC' (79.4%) including 5,700 users of LNG containing COC (11.5% of total study population). Within the 'other cohort' norethisterone accounted for 20% of exposure, drospirenone for 20%, norgestimate for 8%, desogestrel for 6%, gestodene for 5% chlormadinone for 4%, dienogest for 3% and cyproterone acetate for 2%.

Etonogestrel (ENG)

The *Transatlantic Active Surveillance in Cardiovascular Safety (TASC)* was a MAH-sponsored large, multinational, controlled, prospective, observational active surveillance study to characterise and compare short and long-term effects of ENG/EE with non-ENG/EE oral contraceptives and included women who were new users. Participants were enrolled between September 2007 and September 2009. The main outcomes of interest were VTE and ATE.

New users included women who were first ever users of CHCs, switchers (women who switched products without an intake break or with a break of <4 weeks) and recurrent users (women who restarted their CHC after an intake break of 4 or more weeks). Women were further categorised into the ENG/EE group or the 'various other marketed COCs' group, which included COCs containing drospirenone, norethisterone, levonorgestrel (LNG), norgestimate, desogestrel, gestodene, dienogest, chlormadinone and cyproterone acetate.

A total of 33,295 women were enrolled from the US (17,381 women) and five EU countries (15,914 women). Of these, 16,864 women used ENG/EE and 16,431 used a COC. The split between the two groups was relatively equal between the US and EU. Participants were contacted at 6 and 12 months post enrolment and every 12 months thereafter for between 24 and 48 months. Cumulative exposure to ENG/EE was 22,927 women-years and to COCs was 28,252 women-years. The number of confirmed serious adverse drug reactions (ADRs) ranged from 250-270/10,000 and no difference was observed between the groups.

Fifty seven cases of VTEs were observed. The stratification by user type (first ever users of CHCs, switchers and recurrent users) made the number of cases small, but there would appear to be a trend towards a higher incidence of VTE in women who were switchers i.e. had had no break between products or a break of less than 4 weeks.

FDA sponsored study: Combined hormonal contraceptives and the risk of cardiovascular disease endpoints

This retrospective cohort study compared the risk of thromboembolism and other cardiovascular events in new users of ENG/EE with the risk in users of COCs, and also evaluated the risk with the transdermal patch (norelgestromin / EE) and drospirenone-containing COCs. A total of 835,826 women aged 10-55 years formed the initial cohort of women who had received at least one prescription for DRSP/EE, norelgestromin/EE patch, ENG/EE or one of 4 older CHCs (levonorgestrel 15-20µg or 10-30µg EE, norethisterone/EE or norgestimate/EE) with similar low oestrogen levels between January 2001 and December 2007, preceded by at least six months of continuous membership.

The primary objective was to evaluate the risk of thrombotic and thromboembolic events and all-cause and cardiovascular mortality. The analysis used either the 'all user' cohort (current and new users during the study period – and 'new users' (only new users of the COCs of interest during the study period). For the 'all user' analyses the MAH commented that because ENG/EE was approved after the start of the study all women using it would be 'new' users and therefore at high risk of VTE compared with women who had been using the older products long after the period of highest VTE risk.

A comparison of 'all users' in the ENG/EE with those in the LNG/EE group showed age and site-adjusted incidence rates for VTE of 11.9 and 6.6/10,000 respectively and an adjusted hazard ratio (HR) of 1.3 (0.8-2.0). When the analysis was restricted to new users the corresponding incidence rates for VTE remained relatively unchanged for ENG/EE at 11.4/10,000 and increased to 9.2/10,000 for LNG/EE to give an adjusted HR of 1.0 (0.5-2.0).

In a retrospective national registry based cohort study of women in Denmark aged 15-49 years between 2001-2010 the incidence of VTE among all users of ENG/EE was estimated to be 7.8/10,000 women-years and 6.2/10,000 among all users of LNG-containing COCs. The adjusted relative risk of VTE for the comparison of ENG/EE with LNG/EE was 1.9 (1.3 – 2.7) (Lidegaard *et al*., 2012).

Across all MAH sponsored and non-MAH sponsored safety studies of the ENG/EE vaginal ring, the incidence of VTE among users of the ENG/EE vaginal ring ranged from 0–12.7/10,000 women-years.

In retrospective database studies, the VTE incidence rates for ENG/EE range from 7.8/10,000 women-years to 11.9/10,000 women-years. In prospective studies the adjusted hazard ratio of VTE in ENG/EE users compared with other COC users was 0.8 (95% CI 0.5-1.5), and the adjusted hazard ratio among ENG/EE vaginal ring users vs. LNG users ranged from 1.07 (95% CI: 0.32-3.62) to 1.9 (95% CI: 1.3-2.7).

In addition, a cohort study on the risk of VTE and ATE with ENG/EE has been published (Sidney *et al.,* 2013). An initial cohort of 835,826 women aged 10-55 years and who had at least one prescription of one of four comparator COCs between January 2001 and December 2007 that was preceded by at least six months of continuous membership to the database were identified. The four comparator COCs were LNG containing either 10-20 µg EE or 15-30µg EE, norethisterone or norgestimate. The relative risk for ATE, VTE and mortality in the ENG/EE group did not show significant difference compared with the COCs group.

Overall, it was noted that these data do not provide any new information relating to risk estimates.

Drospirenone (DRSP)

Epidemiological studies that compared the risk of VTE associated with use of DRSP/EE 3mg/0.03mg to the risk with use of CHCs containing LNG reported differing results ranging from no difference in risk to a three-fold increase in risk. The EURAS/LASS (LASS: follow up extension of the EURAS study, Dinger *et al*., 2011) combined database studies found the incidence of VTE in women with or without other risk factors for VTE who used DRSP/EE 3mg/0.03mg to be in the same range as that for users of LNG containing CHCs and other CHCs. The Ingenix study also confirmed a similar incidence of VTE among all of the cohorts. The available results from the latest interim analysis indicate that the risk of VTE and ATE is similar to other contraceptives or LNG-containing CHCs.

From the more recent pharmacoepidemiological studies reviewed, the crude incidence rates for drospirenone and the levonorgestrel and norgestimate comparators are presented (per 100,000 women-years) in the following table:

Table 3: VTE Crude Incidence Rates

Study	DRSP	LNG
Jick and Hernandez, 2011	30.8	12.5
Lidegaard *et al.,* 2011	68.3	55.6
EURAS	90.8	79.6
Parkin *et al*., 2011	23.0	9.1
Lidegaard *et al.,* 2009	78.3	57.9
Sidney *et al.,* 2012	17.5	-
Seeger *et al*., 2007	127.8	-
Gronich *et al*., 2011	86.2	-
Total*	**52.9**	**27.7**

DRSP: drospirenone, LNG: levonorgestrel

*Total calculated as sum events/sum women-years

Some studies have reported an increased risk of VTE with drospirenone compared with levonorgestrel (Parkin *et al.*, 2011; Jick and Hernandez, 2011; FDA 2011, Gronich *et al*., 2011) but others have not (Dinger *et al*., 2007; Seeger *et al.*, 2007).

All identified studies are presented below.

Table 4: Summary of studies on VTE risk with drospirenone vs LNG/EE

Author (date)	Design	Exposure non-users (women-years)	Incidence non-users (100,000 women-years)	Exposure LNG (women-years)	Incidence LNG (100,000 women-years)	RR vs LNG [95% CI]
MAH studies						
Seeger *et al.,* 2007 (Ingenix)	Cohort	NA	NA	NA	NA	1.0 [0.5-1.9]
Dinger *et al.,* 2007 (EURAS)	Cohort	25,767	47	31,415	80	1.0 [0.6-1.8]
LASS 2012	Cohort	102,746	45	57,539	92	1.1 [0.8-1.7]
Independent studies						

Lidegaard *et al.,* 2009	Cohort	7,194,242	30	367,408	55	1.6 [1.3-2.1]
Van Hylckama *et al.,* 2009	Case control	NA	NA	NA	NA	1.7 [0.7-3.9]
Dinger *et al.,* 2010	Case-control	NA	NA	NA	NA	1.0 [0.6-1.8]
Jick *et al.,* 2011	Cohort and nested case-control	NA	NA	521,824	13	2.8 [2.1-3.8]
Parkin *et al.,* 2011	Cohort and nested case-control	NA	NA	482,229	9	2.9 [1.1-7.4]
Lidegaard *et al.,* 2011	Cohort	4,960,730	20	104,251	55	2.1 [1.6-2.8]
Gronich *et al.,* 2011	Cohort	NA	NA	NA	NA	1.7 [1.0-2.7]
Sidney *et al.,* 2013	Cohort	NA	NA	NA	NA	1.6 [1.1-2.2]
	Average	**-**	**36**	**-**	**51**	**-**

In addition since 2001 two meta-analyses have estimated a pooled relative risk estimate for drospirenone versus levonorgestrel and found very consistent pooled estimates.

Table 5: Meta-analyses for the comparison of drospirenone with levonorgestrel

Author (date)	RR [95% CI]
Martinez *et al.,* 2012 4 cohort studies	1.7 [1.1-2.6]
Plu-Bureau (2013) 5 cohort studies + 3 case-control studies	1.7 [1.4-2.2]

One MAH argued that the studies carried out in support of the MA are the most robust (EURAS and Ingenix) and these did not identify an increase in risk with drospirenone relative to levonorgestrel. They consider that all studies that have been published subsequently are subject to limitations that make their findings unreliable.

However, a substantial number of studies plus two good meta-analyses have now evaluated the thrombotic risk with drospirenone containing CHCs. These use a number of different data sources

across different countries and, with the exception of the MAH-sponsored studies (plus the study by Dinger), all consistently show an elevated risk of VTE in drospirenone users relative to levonorgestrel users that was, in most cases, statistically significant. The risk estimates most commonly range between about 1.5 and 2 times versus levonorgestrel. While limitations can always be identified for observational studies, bias and residual confounding are unlikely to account for the entire risk increase that is observed. The Sidney study in particular is considered to provide strong evidence as this analysis was restricted to new users (of which there were almost 140,000 in this cohort study).

Overall, consistent findings support an excess VTE risk with DRSP in relation to LNG.

Norgestimate (NGM)

A review of the literature was conducted that compared the venous thrombotic risk of NGM, with that of other CHCs as well as CHCs containing LNG/EE. In addition studies that have grouped NGM with other OCs have also been reviewed.

A high-level overview of several observational studies on VTE that addressed the differential risk between new users and established users was provided, and include the following:

Multi-national case-control study by World Health Organization (WHO), 1995; Transnational (UK and Germany) case-control study, 1993-1996 (Spitzer *et al*., 1996); Transnational (UK and Germany) case-control study, 1993-1996 (Lewis *et al.,* 1996); Danish case-control, 1994-1995 (Lidegaard 1998); Transnational (UK and Germany) case-control study, 1993-1996 (Suissa *et al.,* 1996); UK GPRD cohort and case-control study 1992-1997 (Farmer *et al.,* 1999); UK MediPlus cohort and case-control study 1992-1997 (Todd *et al.,* 1999); 5 year Danish case-control, 1994-1998 (Lidegaard et al., 2002); US Pharmetrics nested case control study, 2000-2005 (Jick *et al.,* 2006); 10 year Danish cohort study, 1995-2005 (Lidegaard *et al.,* 2009); 10 year Danish cohort study 2001-2010 (Lidegaard *et al.,* 2012). Only most relevant information is discussed hereinafter.

Results for all direct comparisons for HCs containing NGM compared to CHCs containing LGN are summarised below.

Table 6: **Estimates of Venous Thrombosis Risk in Current Users of COCs containing NGM Compared with Users of OCs containing LNG**

Epidemiologic Study	OC comparator	Adjusted Odds Ratio (95% CI)
Lidegaard *et al.,* 2002	LNG	0.4 (0.2-0.8)
Lidegaard *et al.,* 2009	LNG	1.19 (0.96-1.47)
Lidegaard *et al.,* 2012	LNG 30-40 µg	1.09 (0.86-1.38)
Jick *et al.,* 2006	LNG + 30 µg EE	1.1 (0.8-5)
Lewis *et al.,* 1996	LNG	1.85 (0.95-3.58)
Todd *et al.,* 1999	LNG	0.7 (0.2-2.4)
Farmer *et al.,* 2000	LNG 150 µg +EE 30 µg	RR: 1.1 (0.62-2.0) Controlling for year of birth: 1.1 (0.6-2.3) Controlling for 5-year bands: 0.8 (0.3-2.1)

Results were variable across all studies with the point estimates of odds ratios ranging from of 0.4 to 1.85 and most studies did not show significance.

Only the Jick and colleagues (2006) study was specifically designed to compare the risk of NGM/EE with LNG/EE and, unlike many of the other studies, included a large number of exposed cases. The Lidegaard and colleagues (2011) study also included a large number of cases exposed to NGM and was considered to be robust by PhVWP after careful analysis of its methodology. Neither study found a significant increase in VTE risk versus LNG/EE.

In one meta-analysis the pooled relative risk estimate for norgestimate versus levonorgestrel also suggested no increase in risk relative to LNG/EE. However only 4 case-control studies were included and the pooled estimate mostly reflects the data from the Jick study.

Table 7: Meta-analyses for the comparison of norgestimate with levonorgestrel

Author (date)	**RR [95% CI]**
Martinez *et al.,* (2012)	
Case-control studies	**1.1 [0.8-1.5]**

The brandleader MAH (Janssen-Cilag) states that almost all studies showed that there was no difference between the thrombotic risks of CHCs containing NGM compared with LNG. In most of the formal studies of risk there have not been enough users of NGM to arrive at a satisfactory estimate of risk making the position uncertain. Many of the earlier studies used a comparator of NGM + LGN because of their metabolic similarity.

It is agreed that one significant limitation with some of the older studies is that NGM/EE CHCs have variously been categorised as second generation CHCs and combined with LNG and/or norethisterone to increase exposure or categorised as third generation CHCs and combined with DSG and GSD containing CHCs. This makes it difficult, if not impossible, to determine the risk estimate for NGM/EE alone.

A total of 11 studies that provide information on the risk of VTE with NGM/EE have been reviewed of which only one (Jick *et al.,* 2006) was designed to evaluate the risk of VTE with NGM/EE.

In 8 studies the thrombotic risk with NGM/EE was compared directly with LNG/EE. Of these only one, a re-analysis of the Transnational data (Lewis *et al.,* 1996), identified an increase in risk with NGM/EE; the remaining 7 studies found no significant difference in risk between the two.

The totality of the data suggest that the risk of VTE with NGM-containing CHCs is no different from that with LNG-containing CHCs.

Nomegestrol (NOMAC) – Zoely, Ioa

The risk of VTE with nomegestrol-estradiol containing CHCs is not known. In view of the recent introduction of NOMAC/E2 on the market, pharmacoepidemiological studies are not yet available.

In the NOMAC/E2 clinical trials no thromboembolic events have been reported among 3490 women exposed for a total of 2695 women-years, yielding an incidence estimate of 0.0 per 10,000 women-

years(95% CI 0.0 - 13.7). No thromboembolic events have been reported in other ongoing MAH-sponsored studies (N=5743).

However clinical trials were not particularly designed for studying the occurrence of thromboembolic events and therefore no conclusion can be drawn from these studies.

When combined with estradiol, nomegestrol seems to affect coagulation in the same way as the levonorgestrel/ethinylestradiol combination. However, it remains to be elucidated if newer CHCs with estradiol have a similar VTE risk.

A large prospective observational post-marketing study, CELINA, is being conducted as a post-approval safety study. The primary objective of the study is to assess cardiovascular and other health risks associated with short and long-term use of NOMAC/E2 compared with LNG-containing oral contraceptives during standard clinical practice. The protocol of this study is currently under discussion with the PRAC and CHMP.

Norelgestromin (NGMN)

A literature review was conducted, including the studies: Boston Collaborative Drug Surveillance Program (BCDSP) Study, I3 (Ingenix) Study, Lidegaard 2012 Study, PharMetrics Study, MarketScan, FDA Study.

For VTE, the results were variable across studies, with point estimates of the odds ratios ranging from 1.2 to 2.2. Methodological differences among the studies could account for some of the variability, although the expected direction of the influence of these design factors is not clear. Variability is expected in most situations in which epidemiologic studies address the same question. The Ingenix and BCDSP studies showed no consistent differences in the estimated odds ratios (or incidence rate ratios) across age groups. Specifically, there was no clear pattern of a higher relative risk among women aged 40-44 than in the other age groups.

Martinez and colleagues (2012) conducted a meta-analysis from a systematic review of studies published between January 1995 and April 2010 aimed at determining the effect of combined hormonal contraceptives on the risk of venous thrombosis. Three case-control studies (Jick *et al*., 2006, 2007, Cole, 2008) provided data on the risk of VTE in users of CHCs with NGM or its derivative, NGMN, according to administration route; that is comparing transdermal patch to oral administration. The OR was 1.18 (95% CI: 0.73-1.89). The analysis showed no significant increase in risk for the NGMN/EE patch (EVRA) as compared to oral administration of a combination of EE and the related progestogen NGM.

Gestodene (GSD)

Pharmacoepidemiological studies have been conducted to assess the VTE risk with gestodene containing CHCs compared with other CHCs, including levonorgestrel containing COCs. Most studies have used data derived from one of four databases: WHO, Transnational, the UK General Practice Research Database (GPRD) or the Danish National Patient Registry. Most studies were conducted before 2001, and were previously evaluated. The best estimate of the magnitude of the relative risk was in the range of 1.5 to 2.0.

The study by Lidegaard *et al* (2011) that covered the period 2001-2009, found adjusted rate ratios of 2.1 (1.6-2.8) and 2.2 (1.7-3.0) for gestodene and desogestrel vs. levonorgestrel respectively. Compared with non-users, an adjusted rate ratio of 4.2 was obtained for both gestodene and desogestrel. The main criticism of this study was that it was unable to adjust for Body mass index (BMI)

and family history. However, as stated by the authors, although these are important risk factors for VTE they have not been found to act as substantial confounding factors in epidemiological studies. The findings of the Lidegaard et al 2011 study confirmed previous estimates of an increase in risk with gestodene or desogestrel CHCs compared with LNG containing CHCs, for example the van Hylckama Vlieg and colleagues study (2009, MEGA) and previous studies by the Lidegaard group.

Dinger and colleagues (2007, EURAS study) found an increased point estimate for the risk of VTE with gestodene or desogestrel compared with levonorgestrel. However, the confidence intervals for these results included 1. This study was primarily designed as a comparison of drospirenone vs. levonorgestrel or other OCs – with a the post-hoc comparison for gestodene/desogestrel. This study has limited power, with a total of 118 VTEs recorded and only 4 and 18 in gestodene and desogestrel users respectively.

Reference was made to the study by Heinemann and colleagues (2010) as evidence for a lack of an increase in VTE risk with gestodene compared with other COCs. However, this MAH-sponsored study had major flaws precluding its consideration as supportive evidence for a lack of increased VTE risk with gestodene, in particular the inadequate definition of the comparator group, the lack of consideration of duration of use, and the small number of cases recorded in users of levonorgestrel.

Overall, the recent information serves to strengthen the conclusions reached at that time. Overall the conclusion is that there is a 1.5-2 times increase in risk of VTE with gestodene compared with levonorgestrel.

Chlormadinone (CMA)

Eleven clinical trials, eight non-interventional studies, and seven other publications were identified.

In the 11 clinical studies with monophasic CMA/EE 5 VTE and 0 ATE events were recorded. In the eight non-interventional studies which included a total of 65,952 subjects and 416,534 cycles corresponding to more than 32,000 woman-year exposure, the MAH identified 7 VTE and 1 ATE events with CMA/EE. None of those events were fatal during the observational period of the studies. From the seven publications that included CMA/EE, a total of 8 VTE and 1 ATE events were reported.

The MAH could not identify any publications on studies that directly compared the risk of VTE in users of CMA/EE with LNG/EE. As a result the MAH compared the published incidences of VTE in LNG/EE users in pharmacoepidemiology studies against a pooled incidence for CMA/EE, derived from phase II and III clinical studies and post-marketing studies.

Such a comparison is not considered to meet the current requirements of the evaluation of the relative risk for thromboembolic events. The data used to derive the incidence estimates for the two different progestogens are highly heterogeneous, being collected using completely different study designs with different objectives, different analysis plans, over different time periods, in different populations, with and without consideration for confounding factors. Only one of the MAH's clinical studies included a placebo group and so there is no internal validation within their studies making it difficult to make any judgements about the reliability of absolute incidence estimates for CMA/EE. The large range observed suggests that even within the MAH's studies there is substantial variability.

A number of the estimates for LNG/EE in the published studies selected by the MAH relate to formulations with different estrogen content (up to 50µg) and so cannot be viewed as an equivalent comparator. In addition the wide range of the confidence intervals for many of these estimates suggests that the number of cases they are based on is small.

In view of the significant limitations of the data and the absence of any direct comparison between LNG and CMA-containing COCs on the risk of VTE or ATE events no conclusions can be made on the

risk of VTE with CMA/EE. Overall, the cited studies do not allow assessment of the VTE risk associated with CMA.

Desogestrel (DSG)

Details have been provided on a MAH-sponsored study, namely The Transatlantic Active Surveillance in Cardiovascular Safety of ENG/EE (NuvaRing, TASC) study, as well as a review of the available literature including the WHO case-control study (WHO, Lancet 1995, Poulter, 1995),the Transnational case-control study (Spitzer *et al.,* 1996, 2002, Suissa *et al*, 1997, 2000, Lewis et al, 1999), Dutch and Danish and German case-control studies(van Hylckama Vlieg *et al*., 2009 Lidegaard *et al*, 2002; Heinemann *et al*, 2002), PharMetrics study (Jick and Hernandez, 2011), Danish registries (Lidegaard *et al*, 2009, 2011)), EURAS study (Dinger *et al,* 2007) and a number of metanalyses (Hennessy *et al*, 2001; Martinez *et al,* 2012; Manzoli *et al*, 2012). In addition the MAH refer to an FDA response to Citizen Petition concerning third generation COCs dated 11 January 2013.

In the large prospective cohort study TASC, the incidence of VTE among users of COCs containing either DSG or GSD was approximately 10.6/10,000 women-years, incidence of PE was 4.2/10,000 women-years, incidence of ATE was 4.2/10,000 women-years (stroke and MI individually: 2.1/10,000 women-years). In published retrospective cohort studies the incidence of VTE among users of DSG-containing COCs ranged from 5 – 6.5/10,000 women-years, incidence of stroke from 1 – 3/10,000 women-years and incidence of myocardial infraction (MI) from 0.6 – 1.4 / 10,000 women-years.

The risk of VTE in users of DSG-containing COCs compared with users of levonorgestrel containing COCs ranges from no elevation in VTE risk to 1.5- 2 fold increase in risk. The variability in estimates can be accounted for in part by methodological differences across studies. Limitations in retrospective database studies have the potential to distort risk estimates by introducing bias. In general, the studies that have adequately controlled for duration of use and other important potential confounders and used confirmed cases provide the most reliable estimates of VTE risk.

The study by Lidegaard and colleagues (2011) is an important confirmatory study, as it involved high exposure and a relatively high number of events (4307). This study covered the period 2001-2009, using the data from 1995-2001 to inform the classification of new users/new starters/never users, among others. This study found adjusted rate ratios of 2.1 (1.6-2.8) and 2.2 (1.7-3.0) for gestodene and desogestrel vs. levonorgestrel respectively. Compared with non-users, an adjusted rate ratio of 4.2 was obtained for both gestodene and desogestrel. The main criticism of this study was that was unable to adjust for BMI and family history. However, as stated by the authors, although these are important risk factors for VTE they have not been found to act as substantial confounding factors in epidemiological studies.

The larger, well conducted studies (Lidegaard *et al*., 2011) and the case-control studies that included greater numbers of cases treated with relevant COCs, as well as the meta-analyses, have consistently demonstrated an increased risk associated with DSG compared with levonorgestrel. Overall the PRAC considered that the information provided strengthens the conclusions that the risk of VTE with DSG is increased compared with levonorgestrel.

Levonorgestrel, norethisterone and non-CHC users

The incidence rates of VTE in non-pregnant, non-CHC users has been assessed and the range slightly revised to 1-3 VTE per 10,000 women-years, with an average of about 2 VTE per 10,000 women-years.

From a number of studies that found between a 2.3 to 3.6 fold increase in risk for the comparison of levonorgestrel CHCs with non-use, an average 3-fold increase in risk was used to estimate the incidence rate in users of levonorgestrel CHCs.

The estimated incidence rate for use of levonorgestrel-containing CHCs is therefore 5-7 per 10,000 women-years, with an average of 6.

The incidence of VTE with use of the non-levonorgestrel CHCs was estimated by extrapolation from the average incidence rate for levonorgestrel-containing CHCs and the average relative risk estimates observed for each of the non-LNG progestogens.

Comparison of VTE risk between norethisterone and levonorgestrel has been performed in 2 studies: GPRD (Farmer *et al.*, 2000) and Danish registry studies (Lidegaard *et al,* 2009, Lidegaard *et al,* 2011). Findings from both studies were consistent:

- In the GPRD study (nested case-control) including 261 cases and 986 controls matched for practice and year of birth between 1992 and 1997, VTE risk with norethisterone was similar to that with levonorgestrel (adjusted OR= 0.3 (0.1-1.0)) (Farmer *et al,* 2000);

- In the Danish registry study, including 1,296,120 women (8,010,290 women-years), VTE risk with norethisterone was also similar to that with levonorgestrel (adjusted OR= 0.76 (0.36-1.60) (Lidegaard *et al*, 2011).

The revised range of incidence rates for each of the studied progestogen-containing CHC as well as for non-users and levonorgestrel-containing CHCs, are reflected in the table below.

Table 8: Risk of VTE with combined hormonal contraceptives

Progestogen contained in Combined hormonal contraceptive	**Relative risk vs LNG**	**Estimated incidence (per 10,000** women-years**)**
Non-users	--	2
LNG	Ref	5-7
NGM/[norethisterone]	1.0	5-7
GSD/DSG/DRSP	1.5-2.0	9-12
ENG/NGMN	1.0-2.0	6-12
CMA/ DNG(EE)/DNG(E2)/ NOMAC(E2)	unknown	unknown

Additional information

Eudravigilance

The EMA performed a study of the reported clinical risk factors and contraindications for venous and arterial embolic and thrombotic in case reports originating from EEA countries and reported to the Post-Authorisation module of EudraVigilance in association with combined hormonal contraceptives (excluding first generation).

The data has been stratified by age and BMI for each of the substances; however, this is unlikely to show much other than a reflection of the distribution in prescribing by that parameter. For example the data for norethisterone would seem to suggest that 64% of cases of VTE or ATE occurred in women over the age of 50, implying that the risk of these events is at its highest in older women. Whilst this is not excluded it is more likely to indicate that older women are preferentially prescribed this second generation drug. Without age-dependent exposure data it is difficult to draw conclusions. Similarly, when stratified by BMI it would appear that the risk of thrombosis is greatest in women with a BMI <30kg/m^2. However, this may alternatively reflect less prescribing in women with a BMI >30kg/m^2.

The reported risk factors suggest that many women who smoke still use CHCs, however their level of smoking is not known. One of the next most common reported risk factors is the presence of hereditary or acquired predisposition (coagulopathy disorder) however it is likely that this is only determined during the diagnostic process and so could not have influenced the prescribing decision.

However, with the possible exception of demonstrating that contraceptives containing levonorgestrel, noethisterone and dienogest are, reassuringly, prescribed more commonly to older women it is difficult to draw conclusions. For drospirenone the proportion of reports of VTE in which BMI was reported was 5% for women with a BMI>35kg/m^2 and 3% for women with BMI >40kg/m^2. This compares with 12% and 3% respectively for the corresponding BMIs with levonorgestrel. Though subject to strong limitations this may indicate that drospirenone is not being unduly prescribed for women who are obese.

Analysis of IMS data on combined hormonal contraceptive

A retrospective database analysis of the prescription patterns of the latest generations of CHCs versus levonorgestrel-containing CHCs in three large EU countries (France, Germany and UK) covering the period 1 January 2002 to 31 December 2011 was performed.

The study included women 15 - 49 years old, recipients of at least one prescription of combined hormonal contraceptives containing levonorgestrel and non-levonorgestrel CHCs as recorded during the study period in the IMS Disease Analyser data of France, Germany and the UK.
The selection of prescriptions for combined hormonal contraceptives was based on the following progestogens:

- *2nd generation* - levonorgestrel, norethisterone, norgestrel
- *3rd or 4th generation* – desogestrel, gestodene, norgestimate, etonogestrel, drospirenone, dienogest, chlormadinone, nomegestrol, norelgestromin

The age of recipient at the time of prescription is computed from the year of birth.

Despite the limitation of the data sources, the results of this study showed different patterns of prescription within the European countries. Throughout 2002-2011 prescribing of 3rd or 4th versus 2nd generation contraceptives (as defined above) was between 30% and 40% of women in France and the UK, while it was between 50% and 70% of women in Germany. The ratio of 3rd or 4th versus 2nd generation contraceptives varies more with age in Germany and the UK than in France.

Across all countries an increased rate of prescription of the latest contraceptives was observed during the past decade. This might be partially explained by a higher percentage of new users of latest progestins in the UK (and to a lesser extent in Germany), together with a high number of patients switching from levonorgestrel-containing CHS to the other progestins in Germany.
In conclusion, this study shows lower usage of 3rd and 4th compared to 2nd generation combined hormonal contraceptives in France and the UK throughout a 10 years period and in all age groups.

IMS MIDAS Data

Additional information from IMS MIDAS has been used to establish a breakdown of contraceptive use for five EU member states, for the year 2012. These data result from an analysis on contraceptive market and concerning some of the European countries with the largest use (France, Germany, UK, Spain and Italy).

The results of this analysis, clearly demonstrate differences in the usage patterns of the type of CHCs between the five countries. It appears that the use of levonorgestrel containing CHCs is around 50% and the other half is split between the rest of the progestins in France. In UK, percentage of the latest progestins-containing CHCs being used is approximately 50%, 40% of levonorgestrel containing CHCs and 10% of the rest. In Germany, usage patterns reveal a percentage of 28.5% of levonorgestrel containing CHCs against 64.3% of the rest of progestins. The most obvious difference appears with Spain and Italy with more of the latest progestins are being used, corresponding to 77% for Spain and 90.4% for Italy.

Effect of dose (<50µg) of ethinylestradiol on VTE risk

There is some evidence from randomised controlled studies that doses of oestrogen below 30 µg are associated with higher rates of bleeding pattern disruptions and higher rates of early trial discontinuation overall and due to adverse events such as irregular bleeding, as well as an increased risk of bleeding disturbances (Gallo, Cochrane Library 2011). By comparison, few studies (and no randomised trials) have compared the thromboembolic effect of oestrogen at doses <50µg.

In a recent study, Lidegaard and colleagues (2009) concluded that the risk of VTE decreases with decreasing oestrogen dose. However, the confidence intervals are overlapping for the different dose ranges in all cases. In some cases, no reduction is observed.

In the other Lidegaard and colleagues study (2011) the difference in risk of VTE due to a reduction in dose from 30-40 µg to 20 µg EE in CHCs containing DSG and GSD are bordering on statistical significance for some comparisons but there is no difference in any of the comparisons with drospirenone, despite the large numbers of cases.

In the Dutch MEGA cohort study by Van Hylckama a direct comparison of the risk of VTE with levonorgestrel-containing pills containing 20 µg or 30µg EE found no difference (RR 1.1 [0.4-3.1]). When preparations containing desogestrel or gestodene plus 20µg EE were compared with preparations containing LNG plus 30 µg EE a statistically significant reduction in VTE risk was observed; however,

interpretation of the results is complicated by the fact that both the dose of oestrogen and type of progestogen are different.

After assessing all the submitted data the PRAC considered that there may be some evidence for a further reduction in risk of VTE with a decrease in dose of ethinylestradiol from 30-40µg to 20µg but the data are not yet sufficiently robust to draw definite conclusions and make recommendations.

B. Effect of progestogen on risk of ATE

The ATE risk is presented as overall data and studies here.

The risk of ATE in young women is lower than the risk of VTE and so most studies evaluating this risk have been carried out with gestodene, desogestrel and norgestimate, which have the greatest cumulative exposure.

When desogestrel and gestodene were first marketed there was some expectation that their associated risk of ATE would be lower than with levonorgestrel, because of their anti-androgenic properties. It is to be noted that in their responses, no company has claimed a difference in the risk of ATE according to progestogen.

The study by Lidegaard and colleagues (2012) is the most significant study to evaluate the risk of ATE (both ischaemic stroke and MI). It is the largest epidemiological study of ATE - including a cohort of approximately 1.6 million women, over 14 million women-years of exposure and a high number of events (ischaemic stroke, n=3311; MI, n=1725). Although the risk of ATE with the different progestogens was not directly compared, similar, statistically significant increases in risk of ischaemic stroke were observed for users of the six progestogens included versus non-users (RRs ranging from 1.5 to 2.2). The risks for MI were similar to those for ischaemic stroke, with statistically significant relative risks ranging from 1.7 to 2.3 compared with non-use. The only finding that was not significant at the 95% level was that for MI risk with norgestimate (RR 1.3 [0.9-1.9]).

Overall, the PRAC considered that there is sufficient evidence to demonstrate that CHCs increase the risk of ATE (both ischaemic stroke and MI) versus non-use but there is insufficient evidence to demonstrate any difference between the different generations of CHCs.

Effect of dose (<50µg) of EE on risk of ATE

One of the first studies to consider whether the risk of ATE is influenced by the dose of EE was a 5 year case control analysis by Lidegaard and colleagues (2002) on the effect of CHCs on cerebral thromboembolic attack (CTA). Compared with non-users the risk of CTA was very similar for both the 30-40 µg EE dose (adj OR 1.6 [1.3-2.0]) and the 20 µg EE dose (adj OR 1.7 [1.0-3.1]) for all CHCs with a corrected OR for the direct comparison of 1.1 (0.5-2.2). Similarly, a reduction in EE dose from 30-40 µg to 20 µg in preparations containing desogestrel or gestodene only slightly increased the risk of CTA with both.

From the studies of MI, the Lidegaard and colleagues (2012) study found a trend for decreasing risk with decreasing oestrogen dose. However, in these indirect comparisons all 95% confidence intervals were overlapping.

The PRAC considered that while there is evidence to suggest that the risk of ATE with regards to the dose of oestrogen in CHCs is reduced at doses less than 50µg, the evidence for a further reduction in risk at doses of less than 30-40 µg is sparse and not conclusive for any arterial thromboembolic outcome.

Ad hoc expert group meeting

As part of this review on CHCs, the PRAC sought advice of an ad-hoc expert group on the tolerability and safety of these medicinal products, as well as on how to best manage the VTE and ATE risks, in particular in term of communication to healthcare professionals and patients.
Among other conclusions, the experts recognised that the risk profile of the different products is not sufficiently known at the level of healthcare professionals, hence patients, in daily practice and that a better knowledge of VTE and ATE risks would allow an early diagnosis of those adverse reactions. It was felt that improved communication on the risks and dialogue with the prescriber should be encouraged to fully understand the needs of patients, their lifestyle as well as their risk factors and close monitoring and follow-up of women who have some inherent risk was highly recommended by the experts.

Conclusions on Safety

The PRAC reviewed all available data from clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience as well as the views of the *ad hoc* expert meeting on the safety of the CHCs in relation to the thromboembolism.

Known risk factors for VTE include history of VTE, pregnancy, trauma, surgery, immobilisation (e.g. after surgery or long flights), obesity and smoking (i.e. all situations of a pro-thrombotic state). Also there are certain hereditary thrombophilic defects that increase the risk. Checking personal and family history of VTE before prescribing combined CHC medicinal products is, therefore, recommended in the product information of the products.

The recent review confirmed previous understanding of the level of VTE risk with CHCs containing low dose of ethinylestradiol (ethinylestradiol <50µg) as small, but with slight differences according to the progestogen. No new safety concerns emerged during this review.

There is good evidence for differences between CHCs in their risk of venous thromboembolism (VTE), depending on the type of progestogen they contain. There is no evidence for differences between CHCs in their risk of arterial thromboembolism (ATE).

Many studies have evaluated the risk of VTE (deep vein thrombosis, pulmonary embolism) among users of different CHCs. Based on the totality of the data it is concluded that VTE risk differs between products - with the lower risk products being those containing the progestogens levonorgestrel, norethisterone and norgestimate. For some products (e.g. chlormadinone) there are currently insufficient data to know how the risk compares with the lower risk products. The best estimates of the risk of VTE with a number of ethinylestradiol/progestogen combinations compared with the risk associated with levonorgestrel-containing medicinal products are presented below.

Compared with pregnancy and the postpartum period, the risk of VTE associated with using CHCs is lower.

It has been shown that risk of VTE is highest during the first year a woman starts hormonal contraceptives or when she re-starts after a period of non-use of at least one month (Dinger *et al,*. 2007, Sidney *et al.,* 2013). There is also some evidence to suggest that the risk is increased when a women re-starts after a period of non-use of at least one month. After an initially higher risk during the first year of use, the risk decreases to a constant lower level. The risk of VTE is also higher in the presence of intrinsic risk factors (such as older age, obesity etc.). Risk factors for VTE change over time and an individual's risk should be re-evaluated periodically.

It is known that the risk of ATE (myocardial infarction, cerebrovascular accident) is also increased with use of CHCs, however there are insufficient data available to demonstrate whether this risk varies between different products.

Overall this review confirmed previous understanding of the level of risk of VTE and ATE with CHCs containing low dose of ethinylestradiol (ethinylestradiol <50µg) as small. For VTE there is good evidence for slight differences in the size of the risk according to the progestogen. For ATE the data are insufficient to determine whether the risk differs between CHCs.

2.1.2. Clinical Efficacy

The main benefit of combined hormonal contraceptives is the prevention of unwanted pregnancy. All combined hormonal contraceptives included in this review have been demonstrated to be highly effective in the prevention of conception. CHCs are expected to prevent 997 in every 1000 pregnancies. In everyday use this number falls to 920. There is no evidence for a difference in contraceptive efficacy between CHCs.

2.2. Risk minimisation activities, including communication

The PRAC recommended the following activities to minimise the risks. This includes communication and training activities as well as risk minimisation measures as such.

Amendments to the product information

As a routine risk minimisation measure the PRAC considered that there was a need to strengthen the information in the product information with regards to the risk of venous and arterial thromboembolism and to highlight the difference in the level of risk between products. The PRAC therefore recommended a review of the indication section, the clarification of contraindications and warnings on the risk of venous and arterial thromboembolisms and their symptoms. These changes are further described hereinafter.

With regards to the indication section, it was considered by the PRAC that it should include recommendation for the prescriber to carefully consider individual woman's current risk factors, particularly those for VTE, and differences in risk of VTE between products when prescribing a combined hormonal contraceptive.

The wording on venous and arterial thromboembolism in the warning section was reviewed. It now provides clearer information on the level of risk and how it compares between the different CHCs and details the most important risk factors for ATE and VTE, and known signs and symptoms.

After consultation with healthcare professionals, it was agreed that the summary of product characteristics (SmPC) for each CHC should include a graphical representation of the level of VTE risk associated with that product, levonorgestrel containing products and in non-users.

The PRAC also agreed on changes to the package leaflet (PL), to reflect the changes introduced in the SmPC and ensure that women are fully aware of the level of risk associated with their CHC, of potential risk factors they could have or develop over time and the symptoms of a venous or an arterial thromboembolism. The PRAC recommends that there may be value in testing the readability of the package leaflet to check the clarity of the information to the target population.

Further discussion on the relevant sections of the product information follows further below in the corresponding section of this report.

Information and awareness of the Healthcare professionals and the patients

Since cases of VTE and ATE continue to be reported in women with contraindications and risk factors for thromboembolic risk, the PRAC recommended that educational measures are necessary in order to remind healthcare professionals and women of these considerations.

i. Communication material

- Direct Healthcare professional communication (DHPC)

A draft DHPC has been discussed and core elements agreed to inform healthcare professionals of the results of this review and the latest evidence on the risk of thromboembolism in association with the hormonal contraceptives containing ethinylestradiol or estradiol combined with either: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, norelgestromin, norgestimate or nomegestrol.

- Questions & Answers for women

The PRAC has agreed on core elements for a Questions & Answers document aiming at providing women with answers to questions they may have on the outcome of this procedure and inform on the risk of thromboembolism associated with CHCs, how the level of risk compares between products, and known risk factors, signs and symptoms of venous and arterial thromboembolism*ii. Educational Material*

The PRAC also recommended that educational material should be developed to inform the professionals and women on the risks of thromboembolism associated with combined hormonal contraceptives and to help remind them of the most important risk factors to consider when discussing the most suitable contraceptive method. The PRAC also recommended educational material for women to be aware of the risks and remain vigilant for signs and symptoms.

Educational material qualified as additional risk minimisation measure should be reflected in the risk management plan of the product, where applicable.

- Checklist for prescribers

The PRAC recommended the development of a checklist for prescribers to use to facilitate the discussion between the prescriber and woman who is being prescribed a CHC. This checklist is intended to be used by general practitioners, nurse prescribers, midwives, gynaecologists and staff of family planning clinics, to initiate a discussion with women about the suitability of a treatment with a CHC. This checklist should be used in conjunction with the Summary of Product Characteristics.

- Information card for women

The PRAC recommended a small information card as additional risk minimisation activity to provide concise information on the important signs and symptoms of VTE and ATE and when to seek medical attention.

Training of relevant MAHs' staff

The MAHs should ensure that their relevant staff are adequately trained and have a good understanding of the level of risk associated with CHCs. The MAH's staff who may be contacted by interested parties following the outcome of this referral should receive appropriate training to be able to adequately inform stakeholders once the procedure is completed; the PRAC also emphasized the

importance of adequate training for the relevant staff in all aspects related to their area of work, in accordance with official guidance from competent authorities.

Effectiveness of the risk minimisation activities including communication

The PRAC recommends that the MAHs work together and conduct joint survey-based studies to measure the success of providing and understanding all core communication and educational materials. Studies should be ideally performed at baseline, prior to educational interventions, and once the interventions are embedded into clinical practice. It is also recommended that periodic follow-up studies are conducted to investigate the maintenance of effect.

PHARMACOVIGILANCE ACTIVITIES

Submission of data

The MAH of dienogest will conduct and submit a pooled analysis of all their post-authorisation safety studies on the risk of DNG/EE versus LNG/EE. This should include a calculation of the power of the analysis. The analysis should be provided to member states within three months after Commission Decision

Post-authorisation safety study (PASS)

An imposed post-authorisation safety study to compare the risk of VTE with CMA/EE containing CHCs versus LNG/EE containing CHCs was recommended by the PRAC. The protocol of this study should be submitted within six months after Commission Decision for agreement. The final study report should be submitted by end of 2018.

The medicinal products containing chlormadinone will be included in the additional monitoring list according to the legislation.

2.3. Product information

Summary of product characteristics

Section 4.1 Therapeutic indication

[Current indication]

The following paragraph should be added to this section under the currently authorised indications:

The decision to prescribe [product name] should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism, and how the risk of VTE with [product name] compares with other CHCs (see sections 4.3 and 4.4).

Section 4.3 Contraindications

The PRAC confirmed the situations in which combined hormonal contraceptives should be contraindicated and agreed clarified wording. These include patients with presence or risk of venous or arterial thromboembolism, such as history of deep venous 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, high risk of venous or arterial thrombosis due to multiple risk factors.

Section 4.4 Special warnings and precautions for use

The PRAC also recommended for warnings to be included in this section, describing how the risk of VTE with the product compares with other CHCs (when such information is available), as well as a comparison of the level of risk in women using a given CHC, in pregnant women and in the post-partum phase. It was also recommended by the PRAC that these differences in the level of risk are reflected graphically in this section.

This section was also amended to reinforce the message that the decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use or when she re-starts a CHC after a break in use of 4 weeks or more.

The PRAC also recommended a harmonised presentation of the risk factors and symptoms of VTE and ATE for all CHCs included in this review.

Finally, this section now includes a paragraph on medical examination/consultation that provides instructions for healthcare professionals at the time of the medical examination of the patient and before a CHC can be prescribed. This paragraph also provides guidance on how best advise women and how to inform them about the risks of VTE and ATE associated with CHCs.

Section 4.8 Undesirable effects

This section was amended to include the following serious adverse events: venous thromboembolic disorders, arterial thromboembolic disorders.

Package Leaflet

The package leaflet was aligned to the SmPC proposals.

The Product Information of Chlormadinone containing CHCs should also reflect the addition of the product in the list for additional monitoring.

3. Overall discussion and benefit-risk assessment

Medicinal products containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, norelgestromin, norgestimate or nomegestrol are authorised in the European Union as combined hormonal contraceptives (CHCs). These are combined with varying doses of ethinylestradiol (EE) or with estradiol (E2).

In February 2013, the French medicines agency (ANSM) initiated a referral procedure under Article 31 of Directive 2001/83/EC on the basis that the benefit-risk balance of these combined hormonal contraceptives had become unfavourable in the currently authorised indication of contraception due to the increased risk of thromboembolism (TE) and therefore it was in the interest of the Union to refer the matter to the PRAC. The PRAC was requested to give a recommendation on whether the indication of medicinal products containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, norelgestromin, norgestimate or nomegestrol combined with an oestrogen (ethinylestradiol or estradiol) should be restricted and/or any other regulatory measures taken.

The PRAC reviewed all available data from clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience, including responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations, as well as the views of an *ad hoc* expert meeting on the efficacy and safety of the CHCs, in particular in relation to the risk of thromboembolism.

Thromboembolic events are adverse events which usually occur in a vein of the leg (deep vein thrombosis, DVT). When diagnosis is not made and no treatment is started, or when clear symptoms of thrombosis are not identifiable, the clot can move upwards to the lung (pulmonary embolism, PE) or the brain (cerebral embolism, CE). Misdiagnosis is possible, since TE presents with diffuse symptoms and is a rare event in a population of healthy young women. Overall, venous thromboembolic events (VTE) could be fatal in 1-2% of the cases. Known risk factors for VTE include history of VTE, pregnancy, trauma, surgery, immobilisation (e.g. after surgery or long flights), obesity and smoking (i.e. all situations of a pro-thrombotic state). Also there are certain hereditary thrombophilic defects that increase the risk. Checking personal and family history of VTE before prescribing combined CHC medicinal products is, therefore, recommended in the product information of the products.

Many studies have evaluated the risk of VTE and its complications (deep vein thrombosis, pulmonary embolism) among users of different CHCs. The recent review confirmed the previous understanding that the level of VTE risk with CHCs containing low dose of ethinylestradiol (ethinylestradiol <50µg) is small, but differences in the VTE risk were observed between most products depending on the type of progestogen they contain. Based on the totality of the available data the PRAC concluded that the risk of VTE differs between products - with the lower risk products being those containing the progestogens levonorgestrel, norethisterone and norgestimate. For some products (i.e. chlormadinone, dienogest nomegestrol) there are currently insufficient data to establish the risk compares with the lower risk products.

Best estimates of the risk of VTE with a number of ethinylestradiol/progestogen combinations compared with the risk associated with levonorgestrel-containing pills are shown in the table below. For some products (chlormadinone /dienogest/nomegestrol) the relative risk is not known at present. For chlormadinone this will be investigated through a post-authorisation safety study, which is further discussed below. For dienogest and nomegestrol studies are on going and results will be submitted when available.

Table 9: Estimated incidence of risk of VTE with combined hormonal contraceptives

Progestogen in CHC (combined with ethinylestradiol, unless stated)	Relative risk vs Levonorgestrel	Estimated incidence (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
Etonogestrel / Norelgestromin	1.0-2.0	6-12
Chlormadinone / Dienogest/ Nomegestrol acetate (E2)	unknown	unknown

E2 – estradiol;

It has been shown that risk of VTE is highest during the first year a woman starts hormonal contraceptives or when she re-starts after a period of non-use of at least one month (Dinger *et al,*. 2007, Sidney *et al.,* 2013). After an initially higher risk during the first year of use, the risk decreases to a constant lower level. The risk of VTE is also higher in the presence of intrinsic risk factors.

Considering that risk factors for VTE change over time the PRAC noted that an individual's risk should be re-evaluated periodically.

It is known that the risk of ATE (myocardial infarction, cerebrovascular accident) is also increased with use of CHCs, however there was no evidence for differences between CHCs in their relative risk of arterial thromboembolism (ATE). This was also the view of the *ad hoc* expert meeting.

Therefore, on the basis of the available evidence, the PRAC acknowledged that the benefits associated with using a CHC far outweigh the risk of serious adverse events in most women. There was no evidence for differences between these medicinal products in terms of beneficial effects. However, the PRAC recommended some risk minimisation measures, including a strengthening of the wording of the product information to reflect the current knowledge of risks (incidence rate) as well as symptoms for VTE and ATE and clarifying the situations for which these products are contraindicated. In particular, these medicinal products should be contraindicated in patients with multiple risk factors (overweight, smoking, hypertension, increasing age etc.), in patients after major surgery with prolonged immobilisation, and patients with history or hereditary predisposition of thromboembolism. Furthermore, proactive information to communicate the outcome of the present review and to highlight the risk of the thromboembolic events through a direct healthcare professional communication (DHPC) was recommended.

In addition the PRAC imposed a post-authorisation safety in order to better characterise the relative risk of thromboembolic events due to chlormadinone compared to the levonorgestrel-containing medicinal products.

Benefit –risk balance

Having considered all the above, the PRAC concluded that the benefit-risk balance of the medicinal products identified in Annex I/Annex A[*] in the indication of contraception remains favourable, subject to the inclusion of the restrictions, warnings and other changes to the product information agreed. In addition the marketing authorisation holders of chlormadinone should perform a post-authorisation safety study.

The risk of VTE with CHCs differs among products depending on the type of progestogen they contain. Having assessed all the available data, the PRAC concluded that:

- The estimated incidence of risk is lowest with the CHCs containing the progestogens levonorgestrel, norgestimate and norethisterone: it is estimated that each year there will be between 5 and 7 cases of VTE per 10,000 women who use these medicines.
- The estimated incidence of risk is higher with the progestogens etonogestrel and norelgestromin, with between 6 and 12 cases yearly per 10,000 women.
- The estimated incidence of risk is also higher with the progestogens gestodene, desogestrel, drospirenone, with betwee
- n 9 and 12 cases yearly per 10,000 women.
- For CHCs containing chlormadinone, dienogest and nomegestrol, the available data are insufficient to know how the risk compares with the other CHCs.

For comparison, in women who are not using CHCs (no-users) and who are not pregnant, there will be around 2 cases of VTE each year per 10,000 women.

[*] In this review both nationally authorised as well as centrally authorised products were included.

The review also looked at the risk of arterial thromboembolism (ATE, blood clots in arteries, which can potentially cause a stroke or heart attack). This risk is very low and there is no evidence for a difference in the level of risk between products depending on the type of progestogen.

Educational material is being prepared to help women make informed decisions about their choice of contraception. This material will be disseminated at the time of the EC decision after agreement with the national competent authorities. In the meantime, women who have any questions or concerns should discuss them with their doctor at their next routine appointment.

4. Action plan and communication

- Direct Healthcare Professional Communication (DHPC)

The PRAC considered that a DHPC was needed to communicate on the results of this review and provide the latest evidence on the risk of thromboembolism in association with CHCs. The core elements agreed by the PRAC are provided together with the communication plan The MAHs should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent within the agreed timelines after CHMP opinion to general practitioners, family planning clinics, nurses, gynaecologists, all pharmacists (hospital and community), midwives, accident and emergency (A&E) physicians, respiratory/chest physicians, cardiologists, haematologists, anti-coagulant clinics, general medical physicians, stroke physicians, acute medical consultants. This target audience will need to be tailored at a national level to take into account regional differences in healthcare settings.

- Question & Answer for women

The PRAC also considered that a Question & Answer document should be developed to provide women with answers to any questions they may have on the outcome of this procedure and inform on the risk of thromboembolism associated with CHCs, what are the signs and symptoms of a venous thromboembolism and when the risk is higher

5. Grounds for the recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC for the combined hormonal contraceptives containing medicinal products.
- The PRAC reviewed all available data from clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience, including responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations, on the efficacy and safety of the combined hormonal contraceptive containing medicinal products, in particular with regards to the risk of thromboembolism. The PRAC confirmed the known risk of thromboembolism of combined hormonal contraceptive containing medicinal products, and recommended clear labelling of symptoms of thromboembolic events, as well as the risk factors for thromboembolic events.
- The PRAC considered that in view of the currently available safety data, the benefit-risk balance of combined hormonal contraceptives is favourable, subject to restrictions, warnings and other changes to the product information. In particular, these medicinal products should

be contraindicated in patients with multiple risk factors (overweight, smoking, hypertension, increasing age etc.), in patients after major surgery with prolonged immobilisation and patients with history or hereditary predisposition of venous thrombosis. Further changes to the product information will contribute to better inform the healthcare professionals and women on the risk of thromboembolism.

- The PRAC is of the opinion that the benefits of combined hormonal contraceptive containing medicinal products continue to outweigh the risks in the indication of contraception.
- The PRAC considered that further data are required for the combined hormonal contraceptives containing chlormadinone and imposed the conduct of a post authorisation safety study (PASS) to evaluate the relative risk of thromboembolic events due to these products compared to the ones containing levonorgestrel.

The PRAC, as a consequence, concluded that the benefit-risk balance of the medicinal products identified in Annex I/Annex A in the indication of contraception remains favourable, subject to the agreed conditions, restrictions, warnings, other changes to the product information and additional risk minimisation measures.

Appendix 1

Divergent positions to PRAC recommendation

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1356

Combined hormonal contraceptives (CHCs) containing medicinal products

Divergent statement

The undersigned member of PRAC did not agree with the PRAC's opinion recommending that the Marketing Authorisation of combined hormonal contraceptives containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate should varied as stated by the PRAC.

These members are in full agreement with the scientific assessment made by the PRAC and based on the Rapporteur and co-rapporteur reports:

- They share the concerns over the risks of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) associated with those products.

- They agree with the well demonstrated increased risk of VTE observed with all the CHCs and the differences of risk between these contraceptives mainly driven by the type of progestogens.

- They agree with the range of risk as stated by the PRAC and compared to levonorgestrel containing CHC.

- They support the concern during the first ever year of use when the risk is highest and when restarting after a CHC-free interval of at least 4 weeks and for women with risk factors.

- They agree that there is currently no reliable evidence that newer CHCs have any higher beneficial effect or difference in tolerability

The reasons for this divergent opinion rely on the regulatory actions to take forward, focused on the wording of the section 4.1 Therapeutic indications of the SmPC and were as follows:

- The well documented differences in VTE incidence rates among users of different types of CHCs

- The lowest VTE risk is with products containing levonorgestrel, noresthisterone or norgestimate. In spite of previous reviews of benefits and risks of CHCs that have been conducted by European Member States during the past years as well as the CPMP position statement in 2001 together with a warning on VTE risk already being included in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of these products, VTE events of concern (number and seriousness) in the EU still persist.

Taking all these aspects into account, these members considered that there is a need for a clear recommendation in section 4.1 Therapeutic Indications for a targeted population "first ever users or women with an increased baseline risk of VTE".
For these women, these members were in favour of implementing in the "Indication" section of chlormadinone, desogestrel, dienogest, drospirenone, gestodene, nomegestrol, (those with a higher or a yet not sufficiently evaluated VTE risk) a recommendation to prescribe a CHC with a documented low VTE risk (levonorgestrel or noresthisterone or norgestimate containing product) with the aim of reducing the number of VTE events among CHC users, in particular in first ever users or women with an increased baseline risk of VTE.

Marie Louise De Bruin	10 October 2013	Signature: …….....

Jean-Michel Dogné (BE)	10 October 2013	Signature: ……...
Jacqueline Genoux-Hames (LU)	10 October 2013	Signature: ……...
Herve Le Louet	10 October 2013	Signature: ……...
Martin Huber (DE)	10 October 2013	Signature: ……...
Brigitte Keller-Stanislawski	10 October 2013	Signature: ……...
Isabelle Robine (FR)	10 October 2013	Signature: ……...
Amy Tanti (MT)	10 October 2013	Signature: ……...
Sabine Straus (NL)	10 October 2013	Signature: ……...