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Ethinylestradiol/ Chlormadinone Acetate

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Contents

Abstract

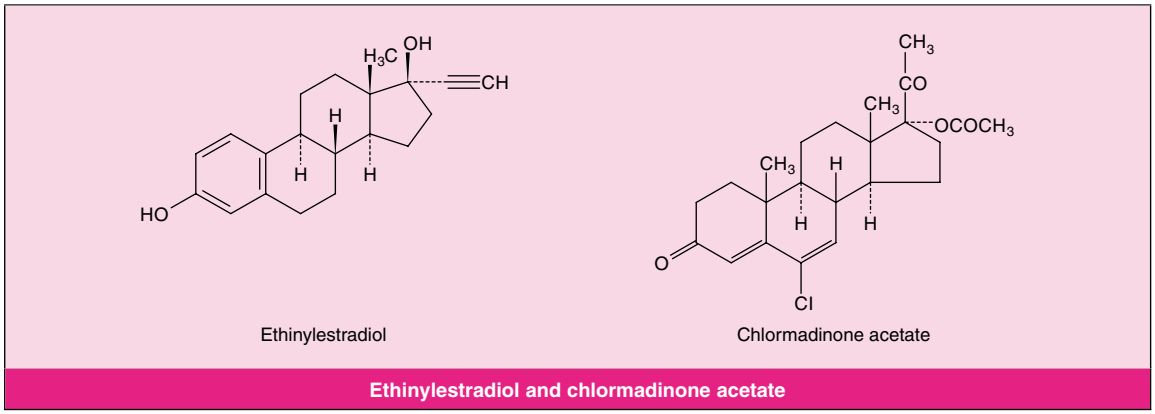
▲ Ethinylestradiol/chlormadinone acetate 0.03/2mg (EE/CMA) is a combined monophasic contraceptive pill with antiandrogenic properties.

▲ In a large, noncomparative, multicentre trial (≤24 cycles of treatment per woman) and two (6- and 12-cycle) postmarketing surveillance studies, EE/CMA was effective in preventing pregnancy.

▲ EE/CMA was significantly more effective than EE/levonorgestrel 0.03/0.15 mg/day in treating women with mild-to-moderate papulopustular acne of the face and related disorders in a randomised, single-blind, multicentre trial.

▲ EE/CMA was well tolerated in clinical trials and the postmarketing surveillance studies. Adverse events were those commonly reported with oral contraceptives. As expected, the most common menstrual disturbances were breakthrough bleeding, spotting and amenorrhoea.

Features and properties of ethinylestradiol/ chlormadinone acetate (EE/CMA)	
Indications	
Prevention of pregnancy	
Mechanism of action	
Inhibition of ovulation by suppression of gonadotropins (EE and CMA)	
Antiandrogenic activity (CMA)	
Dosage and administration	
Dosage in clinical trials	0.03/2mg
Route of administration	Oral
Frequency of administration	Once daily for 21 days of a 28-day cycle
Pharmacokinetic profile (after multiple oral doses of 0.03/2mg in women)	
Mean peak plasma concentrations (EE/CMA)	130 pg/mL/2 ng/mL
Mean time to peak plasma concentration (EE/CMA)	1–2h
Mean elimination half-life (CMA)	36–39h
Adverse events	
Most frequent	Breast pain, migraine/headache, weight gain, gastrointestinal disorder, depression, tiredness



Ethinylestradiol and chlormadinone acetate

Currently over 80 million women worldwide rely on hormonal contraceptives, expecting them to provide optimal contraceptive efficacy and a reliable tolerability profile, with additional benefits to the women's wellbeing.[1] Over the last 30 years, the tolerability of combined oral contraceptives has improved as the dosages of both the estrogen and progesterone components have been reduced.[2] Moreover, modern oral contraceptives differ from older ones, in regard to the progesterone component. Chlormadinone acetate (CMA), in contrast to most progesterones derived from the nortestosterone series, is a progesterone derivative with antiandrogenic properties. This has obvious advantages for women with pre-existing androgen-related skin or hair conditions.[2]

A monophasic combined low-dose oral contraceptive containing ethinylestradiol (EE) 0.03mg and CMA 2mg per tablet (Belara®)[1] has been developed in Germany. This article outlines the pharmacodynamic and pharmacokinetic properties of EE/CMA (with emphasis on the progestogenic component), and its use as an oral contraceptive and treatment for clinical signs of androgenisation.

1. Pharmacodynamic Properties

Published data regarding the pharmacodynamic properties of the combined oral contraceptive EE/CMA 0.03/2 mg/day are limited to those from one randomised, single-blind, comparative, multicentre study, which evaluated its effect on haemostasis.[3] Therefore, data reported in this section regarding EE/CMA have largely been obtained from the manufacturer's product monograph.[4]

The pharmacodynamic properties of the individual components of the combined oral contraceptive are also briefly outlined. Since those of EE are well established,[5-7] the focus is on CMA.

Receptor Binding Affinities

• Receptor binding assays (figure 1) indicate that CMA has high affinity for the progesterone receptor (one third higher than that of progesterone itself).[8] Like progesterone, it has negligible affinity for androgen or estrogen receptors and a low level of binding to the glucocorticoid receptor. In contrast to progesterone, it has no affinity for the mineralocorticoid receptor.[8] At high concentrations, CMA competes effectively with androgens in target tissues to block their effects.[2,8]

Effects on Ovulation and Follicular Development

• With combined hormonal contraceptives such as EE/CMA, the estrogen and progesterone compon-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

ents act synergistically on the hypothalamic-pituitary system.[9] EE lowers follicle-stimulating hormone (FSH), thus preventing follicular development and the rise of circulating estradiol, the proposed stimulus for the preovulatory release of luteinising hormone (LH).[9] In addition, EE maintains the endometrium and helps to prevent breakthrough bleeding. At its ovulation-suppressing dose, CMA suppresses or disrupts the endogenous gonadotropin secretion profile, thus inhibiting follicular growth and maturation.[8,10,11] In particular, CMA suppresses the preovulatory LH peak.[8,10-12]

- When administered without estrogen, the daily dose of CMA required to ensure inhibition of ovulation is 1.5–2mg.[8]
- In a phase II trial, EE/CMA 0.03/2 mg/day effectively suppressed the LH/FSH peri-ovulatory peak in 22 women.[4] A reduction occurred in median FSH (from 6.4 IU/L at baseline to 4.8 IU/L at cycle 3) and LH (from 9.4 to 7.7 IU/L) levels during the follicular phase, with levels of FSH ≤10 IU/L and LH ≤20 IU/L occurring in most women throughout the three cycles. Another study in 22 women showed that, during the luteal phase, a reduction occurred in median LH (from 5 IU/L at baseline to 1.9 IU/L at cycle 6) and FSH (from 3.8 to 2.6 IU/L) levels, with levels of LH ≤20 IU/L and FSH ≤10 IU/L occurring in all women in cycles 1, 3 or 6.[4]
- EE/CMA 0.03/2 mg/day for 3 cycles arrested ovarian activity and follicular growth and/or showed secondary effects (arrest of endometrium in the follicular phase and a barrier function of the cervical mucus) in 65 of 66 cycles in 22 women in a phase II trial.[4]

Effects on the Endometrium

- CMA induces the transformation of the estrogen-primed endometrium.[8] According to the Kaufmann test, a daily 2mg dose of CMA (20–30mg per cycle) achieves full secretory transformation of the endometrium. Conversely, CMA self-limits the effects of estrogen and its own activity by inhibiting estrogen and progesterone receptors.[13,14] Moreover, long-term administration of EE/CMA 0.05/2 mg/day was not associated with endometrial hyperplasia.[8] Withdrawal bleeding occurred within 2–5 days after the last dose of CMA.[8]
- EE/CMA 0.03/2 mg/day for 3 cycles arrested endometrial change (assessed by transvaginal ultrasound) in the follicular phase in all recipients (n = 22) in a phase II study.[4] The median thickness of the endometrium was 11.0mm during the run-in cycle and 5.0mm during EE/CMA administration. This thinning of the endometrium reduces the possibility of embryo implantation.

Effects on Other Reproductive Tissues

- Because of its antiestrogenic effect, CMA dose-dependently reduces the secretions, alters the composition and increases the viscosity of cervical mucus.[15-19] As a result, the penetration of sperm into the cavum uteri is hindered or prevented.[20,21] These effects were greatest with daily doses of CMA 0.3–0.5mg.[2]
- Once-daily CMA 0.5mg reduced fallopian tubular motility.[8]

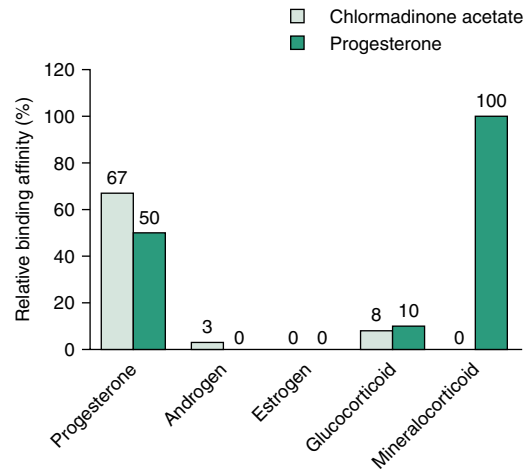


Fig. 1. Relative binding affinities of chlormadinone acetate and progesterone for steroid receptors. The reference compounds (promegestone [progesterone receptor], metribolone [androgen receptor], estradiol [estrogen receptor], dexamethasone [glucocorticoid receptor] and aldosterone [mineralocorticoid receptor]) were assigned an arbitrary relative binding affinity of 100%.[8]

• At a dosage of 2 mg/day, the antiestrogenic actions of CMA induced reductions in the karyopyknotic and acidophilic indices of the vaginal epithelium.[8] This effect was dose-dependently modulated by the estrogen component of combined oral contraceptives.[8]

Antiandrogenic Effects

• EE and CMA have complementary roles in reducing androgen activity.[2,8] CMA acts mainly by blocking androgen receptors,[2,8] as well as down-regulating the number of androgen receptors.[8] EE increases plasma levels of sex-hormone binding globulin (SHBG) levels, thus reducing free testosterone levels; this effect is not antagonised by CMA.[8] Additionally, EE and CMA suppression of gonadotrophin secretion results in inhibition of androgen secretion in the ovaries and adrenal glands.[2,8]

• *In vivo*, CMA demonstrates antiandrogenic activity.[2,22-25] In rats, CMA decreased testosterone-induced weight gain in the prostate and seminal vesicles,[22] produced macroscopic and ultrastructural signs of atrophy and decreased the secretions of male sexual organs,[23] feminised male rat fetuses[24] and suppressed testosterone-induced increases in sebum production in female rats.[25]

• In a randomised, single-blind, multicentre study in women with acne, the median plasma levels of SHBG at cycle 12 were almost twice those at baseline (226 versus 116 nmol/L) in recipients of EE/CMA 0.03/2 mg/day (n = 101); the effect was apparent from cycle 4.[26] In contrast, median levels of plasma SHBG decreased from 96 to 90 nmol/L in recipients of EE/levonorgestrel (LNG) 0.03/0.15 mg/day (n = 98). The statistical significance of these changes was not reported in either group. EE/CMA was effective in reducing clinical signs of androgenisation in this study (see section 3).

Effects on Haemostasis

• In a randomised, single-blind, comparative, multicentre study in women of reproductive age, EE/CMA 0.03/2 mg/day (n = 22) and EE/desogestrel 0.03/0.150 mg/day (n = 23) had a similar effect on haemostatic parameters, with coagulation and fibrinolysis shifting to higher level of activity.[3] Procoagulative activity increased from the run-in cycle to cycle 6, with increases in plasma levels of fibrinogen, factor VII, VIII and XIII activity and prothrombin fragments 1 and 2. Anticoagulative activity was also altered, with increased protein C activity and decreased protein S and antithrombin III activity. In addition, the fibrolytic system was activated, with increased plasmin-antiplasmin complex, fibrinogen cleavage products and D-dimer, and decreased plasminogen-activator-inhibitor and tissue plasminogen activator. The changes in these factors did not exceed the ranges of normal variation and were similar to those previously reported with other low-dose oral contraceptives.[27-29]

Effects on Lipid Metabolism

• In a study in 22 healthy women,[4] EE/CMA 0.03/2 mg/day was associated with increases from baseline in plasma levels of total triglycerides, high density lipoprotein (HDL)-cholesterol, very low density lipoprotein (VLDL)-cholesterol, VLDL-triglycerides and apolipoprotein AI and AII; decreases in low density lipoprotein (LDL)-cholesterol, LDL/HDL ratio and apolipoprotein E were reported. There were no clinically relevant changes in plasma levels of total cholesterol, apolipoprotein B and lipoprotein (a) during the study. Statistical analysis of these changes was not reported.

Effects on Other Metabolic Parameters

• CMA has no mineralocorticoid, antimineralocorticoid or glucocorticoid activity at clinically relevant doses.[8]

• There were no significant changes in mean plasma glucose levels or insulin responses to glucose in

women (n = 24) administered CMA 0.5mg daily for 6 months.[30]

- There were no clinically relevant changes in glycosylated haemoglobin, plasma glucose or insulin levels or evidence of peripheral insulin resistance in women during clinical trials with EE/CMA 0.03/2 mg/day.[4]

2. Pharmacokinetic Properties

The pharmacokinetics of single and multiple doses of oral EE/CMA 0.03/2mg have been investigated in healthy adult women. To date, studies relating to the pharmacokinetic properties of EE/CMA have not been published and, therefore, data presented have been obtained from the manufacturer's product monograph.[4]

The pharmacokinetic properties of the individual components are also outlined. Since those of EE are well established,[5-7] the focus is on those of CMA.

Absorption and Distribution

- Both CMA and EE are rapidly and almost completely absorbed after oral administration, with an absorption half-life of 17 minutes.[4]
- After a single dose of EE/CMA 0.03/2mg in 18 women, the mean peak plasma concentration (C_{max}) of CMA was 1.6 ng/mL[4] and that of EE was 83 pg/mL;[31] both were reached after 1–2 hours.
- During multiple-dose administration of EE/CMA, both components exhibited linear, time-independent pharmacokinetics, without any indication of unexpected accumulation in the plasma.[4] The mean steady-state C_{max} of CMA was 2 ng/mL and that of EE was 130 pg/mL.[4] Steady-state trough plasma concentrations of CMA (0.4–0.5 ng/mL) were achieved within 8–15 days and those of EE (20–40 pg/mL) were reached after 3–10 days. Both remained constant throughout the 6-month study period.[4]
- Both CMA (97–99%)[4] and EE (97–98%)[7] are bound to human albumin. CMA has no affinity for SHBG or cortisol-binding globulin.[8]
- CMA is highly lipophilic and is taken up by the body fat, from where it it released back into circulation.[20]

Metabolism and Elimination

- CMA is extensively metabolised by the liver.[8,22,32] The main metabolites in human plasma are the 2α-, 3α- and 3β-hydroxy derivatives and conjugates thereof; a wide range of other reduced, hydroxylated and deacetylated metabolites also occur. Animal studies indicate that the 3α- and 3β-hydroxy metabolites are associated with antiandrogenic activity;[22,32] this may be due to back-transformation of the metabolites into CMA.[8] The other CMA metabolites are pharmacologically inactive.[8]
- In contrast to many nortestosterone-derived gestagens, CMA does not contain the ethinyl group that *in vitro* inhibits irreversibly the activity of cytochrome P450 mono-oxygenases and 5α-reductase in the liver.[8]
- Because of its extensive fat distribution, CMA is excreted slowly, with a half-life of 36–39 hours after multiple doses. CMA is excreted both renally (45% of a radioactively labelled dose) and in the faeces (41%).[4]
- The glucuronide of 3β-hydroxy-chlormadinone acetate is excreted in the bile and may undergo hydrolytic cleavage and enterohepatic recirculation.[2,8]
- EE is mainly metabolised by hydroxylation at the aromatic ring.[6,7] The major metabolite is 2-hydroxy-ethinylestradiol. EE is excreted in the urine and faeces as glucoronides and sulphates and undergoes enterohepatic recirculation.

3. Clinical Efficacy

The efficacy of EE/CMA 0.03/2 mg/day as an oral contraceptive in healthy women of reproductive age has been assessed in a phase III, noncomparative, multicentre trial (n = 1655, ≤24 cycles per woman, total exposure 22 337 cycles)[33] and in two postmarketing surveillance studies (n = 2620, 12

cycles per woman, total exposure 29 262 cycles[34] and n = 21 820, six cycles per woman, total exposure 125 634 cycles)[35] conducted in Germany. Both postmarketing surveillance studies used a noninterventional design.[33,35] Contraceptive efficacy was assessed according to the Pearl index (the number of pregnancies per 100 women-years of treatment). The effect of EE/CMA on clinical signs of androgenisation was also assessed in these studies as a secondary endpoint.

In addition, the comparative efficacy of EE/CMA 0.03/2 mg/day and EE/LNG 0.03/0.15 mg/day in the treatment of 199 women with mild-to-moderate papulopustular acne of the face and related disorders was assessed in a phase III, 12-cycle, randomised, single-blind, multicentre trial.[26] Acne of the chest (54% of women) and back (50%) was also reported at baseline. A modified Plewig score assessing the number of inflammatory lesions was used to classify the degree of acne.[36]

The combined oral contraceptives were administered for 21 days per cycle, starting on the first day of withdrawal bleeding or menstrual period. This phase was followed by a 7-day tablet-free period.

In the postmarketing surveillance studies,[34,35] exclusion and inclusion criteria were based on the licensed indications and contraindications.

Contraception

- In the noncomparative phase III trial,[33] a total of 12 women became pregnant, giving an unadjusted Pearl index of 0.65 (95% CI 0.36, 1.1). After adjustment for intake errors, concomitant antibiotic intake, diarrhoea and vomiting, the Pearl index was 0.27 (95% CI 0.11, 0.60). The cumulative 12- and 24-cycle pregnancy rates were 0.0023 (95% CI 0.0, 0.0049) and 0.0046 (95% CI 0.00047, 0.0087) per number of EE/CMA recipients when considering pregnancies contributing to the adjusted Pearl index.
- A total of 10[34] and 36[35] women became pregnant during EE/CMA administration in the two postmarketing studies. The unadjusted Pearl indices were 0.4 (95% CI 0.2, 0.8)[34] and 0.344 (95% CI 0.243, 0.466).[35] Pearl indices were 0.04 (95% CI 0.002, 0.2)[34] and 0.076 (95% CI 0.031, 0.143)[35] after adjustment for intake errors and concomitant medication.

Acne and Other Androgen-Related Disorders

- In the comparative phase III trial,[26] a response to treatment (a decrease by at least 50% in the number of papules/pustules per half of the face at baseline by the 12th cycle of treatment; primary endpoint) was reached by significantly more EE/CMA than EE/LNG recipients (59.4% of 101 versus 45.9% of 98 women; p = 0.02). The number of women with no papules or pustules on the face in cycle 12 was 16.5% with EE/CMA and 4.3% with EE/LNG (between-group significance not stated). When analysed according to previous use of oral contraceptives, women who switched from one contraceptive to another had a significantly higher response rate when changing to EE/CMA than EE/LNG (54.8% of 42 versus 32.5% of 40; p = 0.014). EE/CMA was also more effective than EE/LNG in women using an oral contraceptive for the first time (62.7% of 59 versus 55.2% of 58; p = 0.014).
- Moreover, EE/CMA administration resolved papulopustular acne of the chest in 46% of 46 patients and the back in 42% of 43 patients by cycle 12.[26]
- In addition, other androgen-related disorders resolved with EE/CMA treatment,[26] although patient numbers were insufficient for statistical analysis. By cycle 12, resolution of seborrhoea (20 of 25 women), alopecia (6 of 7) and hirsutism (4 of 11) occurred in many patients.
- After 12 cycles, acne and other androgen-related disorders (secondary endpoints) improved in women treated with EE/CMA for >13 cycles in the noncomparative phase III trial.[33] Acne (comedonica, papulopustula and conglobata) of the face and neck improved or completely resolved in 64 and 54% of the 326 women who had these symptoms at baseline. Seborrhoea improved or completely re-

solved in 68 and 58% of the 131 women with this symptom at baseline.[33]

- In the two postmarketing surveillance trials,[34,35] >80% of women who suffered from spots or skin disorders showed an improvement in skin condition (secondary endpoint). For example, in one of the studies,[35] 70% of patients had androgen-related skin disorders at baseline. After six cycles of EE/CMA, these disorders improved in 87% of the patients and completely resolved in 29%. The percentage of women with greasy or very greasy hair also decreased after EE/CMA administration; from 47% at baseline to 14% at cycle 6 in one of the studies[35] and from 51 to 12% at cycle 12 in the other study.[34]

4. Tolerability

Tolerability data for EE/CMA were obtained from the two phase III trials[26,33] and the two postmarketing surveillance studies[34,35] reviewed in section 3.

- Adverse events reported with EE/CMA administration were those commonly associated with combined low-dose oral contraceptives.[26,33-35] The incidences of the most common adverse events in the two postmarketing surveillance studies are presented in figure 2. The adverse events became less frequent as the duration of EE/CMA intake increased.

- There was no major weight change (i.e. a loss or an increase in weight >2kg) in 78.8% of women in the 12-cycle post-marketing surveillance study.[34] Weight gain of 1–2kg or >2kg occurred in 34% and 8.4% of women. Weight loss of 1–2kg or >2kg occurred in 20% and 4.7% of women. In the other postmarketing surveillance study, the mean bodyweight changed from 61.7kg at baseline to 62.0kg after six cycles.[35] Newly occurring or inten-

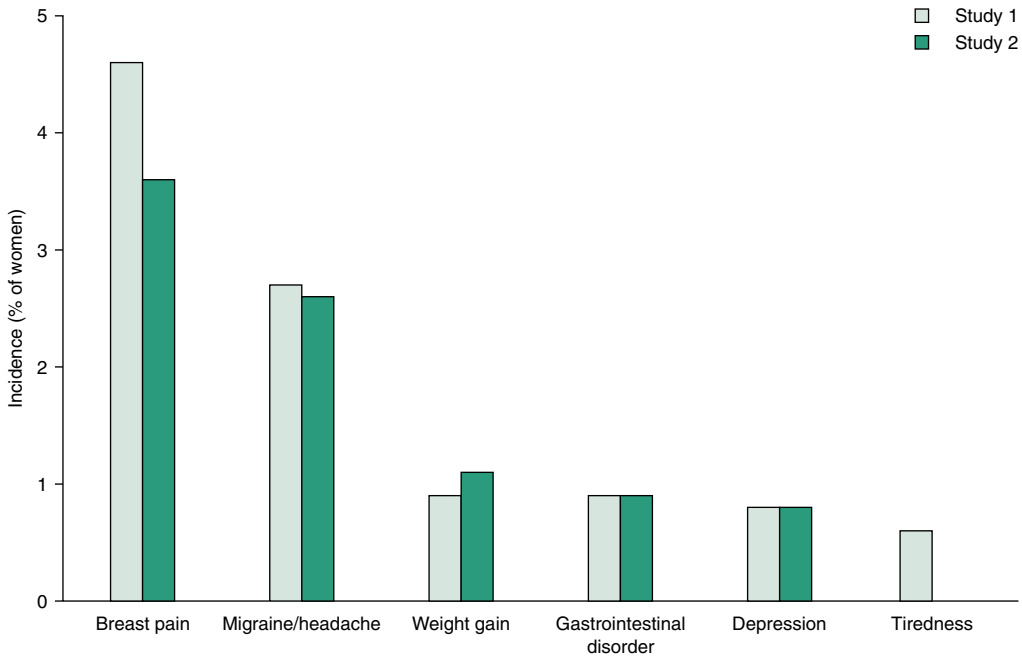


Fig. 2. Incidences of the most common adverse events reported during the use of ethinylestradiol/chlormadinone acetate 0.03/2 mg/day (EE/CMA). In two postmarketing surveillance studies, 2620 (study 1)[34] and 21 820 (study 2)[35] women of reproductive age received 12[34] or 6[35] cycles of EE/CMA for 21 days per cycle, starting on the first day of withdrawal bleeding or menstrual period. This phase was followed by a 7-day tablet-free phase. An adverse event was defined as a symptom that newly occurred or intensified during the observation period.

sified weight gain was reported in 0.9%[34] and 1.1%[35] of patients, respectively (figure 2).

- The rates of withdrawal from treatment in the two postmarketing surveillance studies were 9%[35] and 13%.[34] Reasons for withdrawal included nonmedical reasons (e.g. wish to get pregnant; 3%[35] and 2%[34]), menstrual irregularities (4% in both studies) and other adverse events (including headache, migraine, weight gain, breast pain or depression; 2%[35] and 4%[34]).

- The overall tolerability of EE/CMA was rated as 'good' or 'very good' by 85%[34] and 87%[35] of women in the two postmarketing surveillance studies.

- CMA 0.5 mg/day for 6 months (n = 8) had no effect on serum prolactin levels.[37]

- Regular withdrawal bleeding did not occur in 7.4% of all (22 337) cycles of EE/CMA in the phase III noncomparative trial.[33] When analysed according to previous use of oral contraceptive, first-cycle withdrawal bleeding did not occur in 16.1% of 535 first-time users nor in 11.9% of 1093 women who switched contraceptives. However, the incidence decreased with treatment duration.

In the phase III noncomparative trial,[33] spotting occurred in 11.5% of 22 308 cycles and breakthrough bleeding in 3.5% of 22 308 cycles. The frequency of spotting and breakthrough bleeding also decreased with duration of EE/CMA treatment; 14.4% of 1492 women reported spotting in cycle 3 versus 5.4% of 745 women in cycle 18.[33]

- In the two postmarketing surveillance trials, amenorrhoea occurred in 6.4[34] and 4.3% of women.[35] In all patients, the rates of breakthrough bleeding were 7.1[34] and 6%[35] and of spotting were 26.6[34] and 24%.[35] Intracycle bleeding (spotting and break-through bleeding) decreased with treatment duration (see figure 3). In women who did not have this symptom before initiation of EE/CMA, dysmenorrhoea occurred in 6% in one trial[35] and 88% of EE/CMA recipients were symptom-free in the other trial.[34] In women who had these symptoms in the last two cycles before EE/CMA initiation, intracycle bleeding no longer occurred with EE/CMA in 61.7[34] and 62.2%[35] of patients, amenorrhoea in 89.3[34] and 92.2%[35] and dysmenorrhoea in 66[34] and 67.6%.[35]

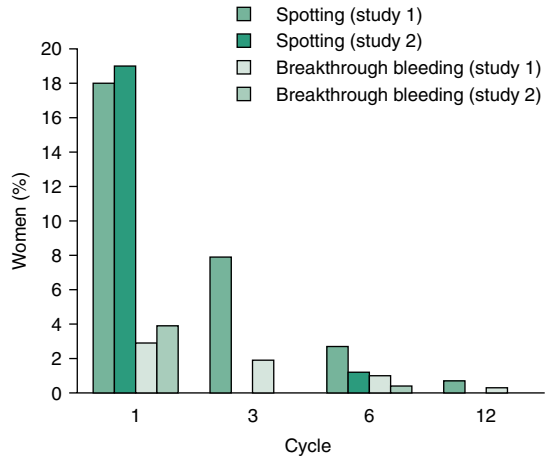


Fig. 3. Incidence of intracycle bleeding in women treated with ethinylestradiol/chlormadinone acetate (EE/CMA). In two postmarketing surveillance trials, 2620 (study 1)[34] and 21 820 (study 2)[35] women of reproductive age received 12[34] or 6[35] cycles of EE/CMA 0.03/2 mg/day for 21 days per cycle, starting on the first day of withdrawal bleeding or menstrual period. This phase was followed by a 7-day tablet-free period.

- Venous thromboembolic events related to study medication were observed in the noncomparative phase III trial (two cases of deep vein thrombosis; n = 1655),[33] and in the 12-cycle (one case of thrombosis in the left thigh; n = 2620)[34] and the six-cycle (one case of superficial leg vein thrombosis and one case of pulmonary embolism; n = 21 820, i.e. 2.1 per 10 000 women years)[35] postmarketing surveillance studies.

5. Dosage and Administration

EE/CMA 0.03/2 mg/day is used in the prevention of pregnancy. EE/CMA tablets are taken for 21 days per cycle, starting on the first day of withdrawal bleeding or menstrual period. This phase is followed by a 7-day tablet-free period.[4]

6. Current Status

EE/CMA is a monophasic combination preparation that was developed in Germany to provide an oral contraceptive that contained a low dose of estrogen.[4] EE/CMA has been marketed in Germany since 1999 for use in the prevention of pregnancy and is currently awaiting approval in other European countries.[2]

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