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# Study to Assess Safety and Tolerability of the Pharmaceutical Composition Based on Diindolylmethane in Patients with Endometrial Hyperplasia without Atypia

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## Abstract

The aim of this clinical trial was to investigate the safety and tolerability of the novel pharmaceutical composition Cineton based on diindolylmethane (DIM). 8 patients with endometrial hyperplasia without atypia were included in the trial. The first experimental group (3 patients) received Cineton at a dose of 400 mg DIM per day and the second group (3 patients) received Cineton at a dose of 600 mg DIM per day. The third group (2 patients) received placebo. The treatment period lasted for 160 days. In addition to the Cineton administration, the patients received a standard hormonal therapy. Safety was assessed by registration of adverse events (AEs), physical examination, laboratory and instrumental testing. No adverse events were registered. There were no discontinuation of Cineton for reasons related to the development of AEs. Use of novel DIM-based formulation was found to be safe and well-tolerated.

## Keywords

3,3'-diindolylmethane (DIM); Clinical study; Endometrial hyperplasia; Safety, Tolerability

## Introduction

Endometrial hyperplasia (EH) is a frequently occurring gynecological disease, which is based on the abnormal proliferation of endometrial glands and stroma. It is known that the endometrial hyperplasia, and in particular its complicated clinical and morphological forms can be regarded as precursors of endometrial cancer (EC). The endometrial cancer high prevalence dictates the necessity to search new pathogenetically grounded methods of its prevention and treatment [1]. In 2012, 319,605 new cases of endometrial cancer and 76,160 mortality cases were registered worldwide. In Russia, the incidence and mortality from endometrial cancer were 16.26 and 8.56 cases per 100,000 population, respectively (data for 2012) [2].

According to the WHO classification (1994), hyperplasia without cellular atypia and hyperplasia with cellular atypia are distinguished. At the same time, the endometrial hyperplasia progression into the endometrial cancer is most likely for female patients with proliferative endometrial glands with cytologic atypia signs. Thus, in the absence of cellular atypia, a malignancy risk of endometrial hyperplasia is not more than 1-3%, while the oncological potential of atypical hyperplasia is up to 30-50% [3]. Women of all ages are at risk for the endometrial hyperplasia development, notably in the presence of additional risk factors such as obesity (especially the visceral obesity), menstrual disorders with a duration of 12 years and more, polycystic ovary syndrome (PCOS), nulliparity, insulin-dependent diabetes mellitus and other severe chronic diseases [4].

An excessive estrogenic stimulation, causing an endometrial proliferation in the absence of an anti-proliferative effect of the progestin, is clearly recognized as the key etiological factor, being the cause of development of both the endometrial hyperplasia with atypia, and endometrial hyperplasia without atypia [5]. The activity of growth factors is also important in the pathogenesis of the endometrial hyperplasia. Thus, in the recent work, [6] the high expression of

epidermal growth factor receptor (EGFR), which generally correlates with the severity of pathological processes in the endometrium, has been detected in female patients with the complex endometrial hyperplasia with atypia. It has been shown previously, that EGF and transforming growth factor  $\alpha$  (TGF- $\alpha$ ) stimulate the growth of endometrial carcinoma cells in vitro and in vivo [7,8]. Other growth factors involved in endometrial carcinogenesis include transforming growth factor- $\beta$  (TGF- $\beta$ ), basic fibroblast growth factor (bFGF) and insulin-like growth factor I (IGF-I) [9-11].

In recent years, the role of epigenetic abnormalities in the progression of endometrial pathological processes has been observed increasingly. The studies [12,13] have demonstrated that promoter hypermethylation of tumor suppressor genes tumor growth MLH1, RASSF1, GSTP1, p16, RAR-b, CDX1 may appear to be the prognostic factor of endometrial cancer development.

The choice of treatment of patients with endometrial hyperplasia depends on the woman's age, the presence of cytologic atypia, planning of pregnancy, as well as the operational risk. The traditional therapeutic approach to the endometrial hyperplasia treatment is the administration of hormonal therapy (endometrial hyperplasia without atypia responds well to progestins), but in most cases of hyperplasia with atypia and in the ineffectiveness of hormonal therapy, standard surgery is prescribed: hysterectomy, salpingo-oophorectomy, or lymphadenectomy [14]. However, it is known that hormonal therapy

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and surgical intervention are often accompanied by some complications as well as contraindications, limiting their use [15]. In addition, there are often relapses of EH after a standard treatment [16].

In recent decades, there has been shown an increased interest in the study of the molecular mechanisms underlying to the pathogenesis of hyperplastic pathological processes in the organs of reproductive system that forms the basis for the emergence of targeted pharmacological agents. Such targeted pharmacological correction means use, in particular, 3,3'-diindolylmethane (DIM) and its metabolic precursor indole-3-carbinol (I3C). It is known that the active substances I3C and DIM normalize the metabolism of estradiol by inhibiting the synthesis of 16 $\alpha$ -hydroxyestrone possessing pronounced carcinogenic properties, as well as inhibit the activity of estrogen receptors by reducing their number in the target tissues [17,18]. It has also been demonstrated that DIM reduces effect of growth factors, which stimulate tumor growth [19]. DIM also induces a selective apoptosis of the tumor cells [20]. A recently discovered DNA demethylating activity of DIM, which leads to the restoration of the tumor-suppressor genes activity, is also of great significance [21].

The drug Cineton, developed by us, include highly bioavailable DIM, placed in nanocontainers of pluronic, which can significantly increase the active substance bioavailability after its oral administration [22]. Safety and efficacy of this formulation has been confirmed in previous preclinical studies [23,24].

The purpose of this study was to evaluate the safety and tolerability of Cineton therapy, which has been used in combination with standard hormonal therapy in female patients with endometrial hyperplasia without atypia.

## Materials and Methods

**Test formulation.** Capsules (3,3'-Diindolylmethane) (100 mg of DIM per capsule, IlmixGroup, Closed Joint Stock Company, Russia), containing kolliphor 407 (pluronic), lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate as excipients; placebo capsules (containing only excipients). The drug Duphaston (Abbott Biologicals B.V., Netherlands): dydrogesterone 10 mg.

**Patients and treatment.** Eight female patients with histologically verified diagnosis of endometrial hyperplasia without atypia at the age from 38 to 50 years were included in the safety study of the drug Cineton.

A screening examination, including an anamnesis collection, physical examination, paypel-endometrial biopsy with histological examination of material, pelvic ultrasound, gynecological smear on flora, tests for infectious diseases, clinical and biochemical blood tests and an electrocardiogram was held 15 days prior to the beginning of active treatment. Premenopausal and menopausal patients, as well as women with uterine submucosal myoma, endometriosis III level, polycystic ovary syndrome, with endometrial cancer or malignancies of any other localization, with arterial or venous thromboembolic disorders, lactose

intolerance, diabetes, diseases of cardiovascular and nervous system as well as renal or hepatic impairment have been excluded from the study. Pregnancy and lactation, a positive test for RW and/or HIV, alcohol abuse, drug or medicinal dependence have also been taken as criteria for exclusion from the study. The use of other medications 30 days prior to the first dose of study medication was not allowed.

After signing the informed consent, the trial subjects were divided into three groups (two experimental groups and one control group). Three patients of the first experimental group were given Cineton at a dose of 200 mg (2 capsules of 100 mg) twice a day (daily dose of 400 mg of DIM) for 160 days. Three patients of the second experimental group received Cineton at a dose of 300 mg (3 capsules of 100 mg) twice a day (daily dose of 600 mg of DIM) for 160 days. Two patients in the control group received 400 or 600 mg of placebo (2 or 3 capsules of placebo twice a day, respectively) for 160 days.

In addition to the Cineton administration, the patients received a standard hormonal therapy in accordance with the recommendations of the National Guidelines for gynecology: dihydrosterone 10 mg/day (1 tablet 1 time per day) from the 16th to the 25th day of the cycle, for a total of 160 days.

The study included three follow-up visits: at study entry, after 80 days and after 160 days after the beginning of the study.

Evaluation of the therapy safety and tolerability was performed clinically and by means of instrumental and laboratory studies. All adverse events (AEs), observed during the study, were recorded in accordance with their nature, severity, duration, and establishing links with the study medication. The safety monitoring of the studied therapy was based on clinical blood test, urinalysis and biochemical blood analysis (determination of glucose, protein, creatinine, total bilirubin, aspartate aminotransferase activity (AST) and alanine aminotransferase (ALT)). The measurement of body temperature, heart rate (HR), respiratory rate (RR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) and electrocardiogram (ECG) registration were also carried out. The fact of medication discontinuation for reasons related to the development of adverse events was considered to be an intolerance.

The study envisaged that the final data analysis would be done at the end of 6 months of therapy. Study was reviewed and approved by the local ethic committee of the Peoples' Friendship University of Russia.

Statistical processing. Chi-square test ( $\chi^2$  test) and Fisher's exact test have been used in order to determine the statistical significance of differences between the groups. The rating of 95% confidence intervals (CI) was carried out using the method of Klopfer-Pearson. Statistical processing of the study results was carried out using the SPSS Statistics 19.0 program.

## Results and Discussion

Eight female patients with a diagnosis of endometrial hyperplasia without atypia at the age from 38 to 50 years participated in the

Presence of adverse events	Number of female patients with adverse events								
	Cineton (400 mg/day) + dihydrosterone (n = 3)			Cineton (600 mg/day) + dihydrosterone (n = 3)			Placebo + dihydrosterone (n = 2)		
	Abs.	Proportion (%)	95% CI	Abs.	Proportion (%)	95% CI	Abs.	Proportion (%)	95% CI
No	3	100	0.0-70.8	3	100	0.0-70.8	2	100	0.0-84.2
Yes	0	0	–	0	0	–	0	0	–

**Table 1:** Number of patients with adverse events in the study groups (6 months of therapy)

study. The patients have previously been analyzed by demographic indicators: height, age, body weight and BMI (body mass index). The data on main vital signs: body temperature, systolic blood pressure (SBP) and diastolic blood pressure (DBP), respiratory rate (RR) and heart rates (HR), well as the ECG parameters, clinical and biochemical blood tests have also been recorded in the course of instrumental studies and clinical analysis. The analyzed parameters were not significantly different in the groups, which made it possible to combine patients in the study groups, considering the sample to be homogeneous.

During 160 days of the study, the first experimental group (three patients) received the drug Cineton at a daily dose of 400 mg of DIM (2 capsules of 100 mg 2 times a day), the second experimental group (three patients) received the drug Cineton at a daily dose of 600 mg of DIM (3 capsules of 100 mg per day). The control group (two patients) received placebo. Besides, all patients received a concomitant standard hormonal therapy (dihydrosterone 10 mg/day from the 16th to the 25th day of the cycle).

Throughout the study period, there was not a single case of adverse events occurrence in the study groups: in the placebo group—0 cases of 2; in the therapy group of Cineton 400 mg of DIM per day—0 cases of 2; in the therapy group of Cineton 600 mg of DIM per day—0 cases of 3. The total number of patients, for whom adverse events were registered, is presented in Table 1 and Figure 1:

In the present study we also analyzed the tolerability of the Cineton therapy, combined with the hormonal therapy by dihydrosterone in patients with endometrial hyperplasia without atypia. According to the study results, there was not a single case of discontinuation of treatment due to occurrence of adverse events in the study groups. The number of adverse events in the placebo group was 0 cases of 2; in the group of Cineton therapy at a dose of 400 mg of DIM per day it was 0 cases of 3, and in the group of Cineton therapy at a dose of 600 mg of DIM per

day the number of adverse events was 0 cases of 3. The total number of patients, for whom the cases of intolerance were registered, is presented below in Table 2 and in Figure 2:

It should be noted that this report on the study results is intermediate, so the number of clinical and laboratory parameters (the level of total protein, albumin, creatinine, glucose, total bilirubin, ALT, AST in the biochemical analysis of blood; indicators PQ, QRS, QT on ECG) for objective reasons (a small number of female patients) has not been evaluated in a comparative perspective from visit to visit. Safety of the drug Cineton application, including the dynamics of change of the above parameters can be assessed after the final results.

Several studies have demonstrated that exposure to I3C or DIM has a pronounced effect against different types of tumors and benign hyperplastic pathological processes of reproductive system. I3C and DIM substances as potential chemopreventive agents were evaluated in different clinical trials phase I and phase II [25-27]. Previously, Reed G.A. *et al.* [25] indicated that daily administration of I3C at doses of 400 and 800 mg was well tolerated by women from a high-risk breast cancer cohort. In 2008 safety and tolerability of the absorption-enhanced DIM formulation BR-DIM (BioResponse-DIM; Boulder, CO, USA) in single increasing doses of up to 200 mg in healthy subjects were determined [26]. According to this study BR-DIM was considered to be well tolerated as all adverse events were defined as mild and not requiring treatment. Findings of another study showed that use of BR-DIM (108 mg DIM daily) for thirty days in post-menopausal women was safe [27].

The drug Cineton containing DIM with pluronic is able to realize unique therapeutic potential of active substance due to its high bioavailability [22]. Safety of this formulation has been confirmed in previous preclinical studies [23,24]. Preliminary results of our current study are consistent with other investigations of safety and tolerability of different formulations based on DIM and its precursor I3C. Our data

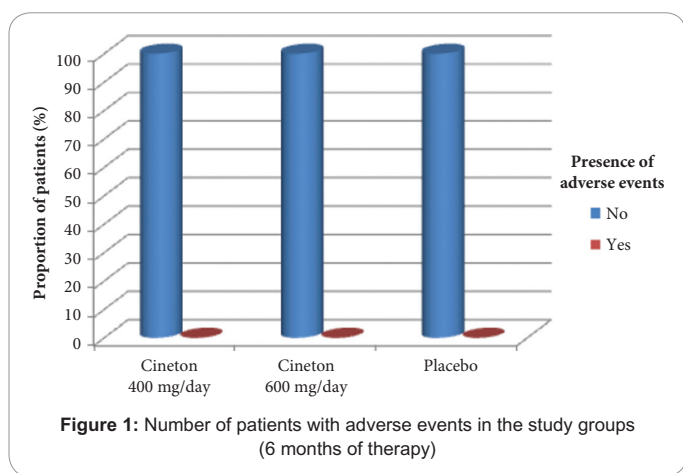


Figure 1: Number of patients with adverse events in the study groups (6 months of therapy)

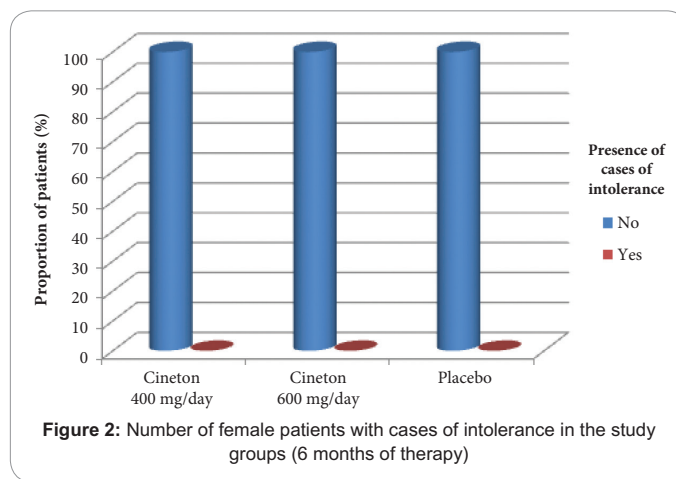


Figure 2: Number of female patients with cases of intolerance in the study groups (6 months of therapy)

Presence of cases of intolerance	Number of female patients with cases of intolerance								
	Cineton (400 mg/day) + dihydrosterone (n = 3)			Cineton (600 mg/day) + dihydrosterone (n = 3)			Placebo + dihydrosterone (n = 2)		
	Abs.	Proportion (%)	95% CI	Abs.	Proportion (%)	95% CI	Abs.	Proportion (%)	95% CI
No	3	100	0.0-70.8	3	100	0.0-70.8	2	100	0.0-84.2
Yes	0	0	—	0	0	—	0	0	—

Table 2: Number of female patients with cases of intolerance in the study groups (6 months of therapy)



demonstrates that use of the drug Cineton with standard hormonal therapy in patients with endometrial hyperplasia without atypia was found to be safe without any indicated side effects.

## Conclusion

The presented results of the safety and tolerability study of the drug Cineton, obtained within the framework of the Phase II of the double-blind, randomized, placebo-controlled multicenter study, are intermediate (the study is scheduled to be completed in 2015). However, based on these intermediate results, already obtained for the eight patients who met the inclusion criteria (diagnosis of endometrial hyperplasia without atypia with indications for conservative treatment), a favorable safety profile of the study medication Cineton can be concluded.

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