Ethinyl Estradiol + Dienogest

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Drug Composition

Low dose composition of Ethinyl Estradiol 30 μg + Dienogest 2 mg belongs to the class of Oral Contraceptives. Ethinyl estradiol is a synthetic estrogen while Dienogest is a novel 19 nortestosterone derived progestin with unique pharmacokinetic and pharmacodynamic actions including anti-androgenic properties.

It was launched in Germany in 1995 and is approved by European Union. Recently, it was approved in India in 2018 by DCGI and indicated for use as an oral contraceptive and in the treatment of mild to moderate acne in women who seek oral contraception.

Pharmacokinetics

Ethinyl Estradiol: Oral ethinyl-estradiol is rapidly absorbed from the stomach and upper intestine, 90% of which is absorbed in the first hour. Peak concentration of ethinyl estradiol is usually 1–2 hours. The bioavailability of ethinyl estradiol is about 25–65%, and the elimination half-life is about 6–27 hours.[1]

Dienogest: The pharmacokinetics of oral dienogest are linear (i.e. proportional to dose). The oral bioavailability of dienogest is about 90%. Dienogest is eliminated relatively rapidly; the terminal elimination half-life was 7.5–8.9 hours after single oral doses of dienogest 2–8 mg or dienogest 2 mg plus ethinylestradiol 30 mg.[2]

Pharmacodynamic Profile

Mechanism of Action: The contraceptive effect of combined oral contraceptives (COCs) is based on the interaction of various factors. The primary mechanisms are inhibition of ovulation (by suppression of gonadotrophins) and changes in the cervical secretion (blocking the entry of sperm into the uterus).

Dienogest has weak antigonadotrophic activity; inhibition of ovulation is thought to occur mainly via peripheral actions rather than central effects on the hypothalamus-pituitary axis resulting in suppression of gonadotrophin secretion.[3] Also, dienogest exerts its anti-proliferation activity by growth suppression of endometrial cells.

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Effects on Carbohydrate Metabolism:

There were no significant increases in glucose levels, glycosylated haemoglobin levels or the insulin/glucose ratio.[4]

Effects on Lipid Metabolism:

Ethinyl estradiol/dienogest significantly increased levels of triglycerides, very low-density lipoprotein (VLDL) cholesterol, high-density lipoprotein (HDL) cholesterol and apolipoprotein A1. There were no significant changes in total cholesterol and lipo-protein (a), while levels of low-density lipoprotein (LDL) cholesterol tended to decrease.[4]

Antiandrogenic Properties:

The combination of ethinyl-estradiol and dienogest reduces serum androgen levels. Following ethinyl estradiol/dienogest treatment, serum levels of sex hormone-binding globulin increased significantly, and there were significant decreases in total and free testosterone levels.[5]

Effects on Haemostasis:

Ethinyl estradiol/dienogest appears to have a balanced effect on the haemostatic system, with minimal stimulation of both procoagulant and fibrinolytic activities.[6]

Two Phase 3 studies were carried out in Poland and Czech Republic to evaluate the safety and efficacy of the combination:

Polish Study [7]:

The efficacy and safety of the low dose monophasic oral contraceptive (OC) combination containing 30 μg of ethinyl estradiol (EE) and 2.0 mg of dienogest (DNG) (EE/DNG) was evaluated in a prospective, open-label, multicentre, uncontrolled, phase III trial. The trial was carried out in five hospitals in Poland, and included 431 healthy women (aged 18-35 years), over 12 cycles, with a total of 4608 cycles. EE/DNG provided reliable ovulation inhibition. No women became pregnant during the trial. The unadjusted Pearl index was 0. EE/DNG provided good cycle control and reduced the incidence of intermenstrual bleedings, the intensity of menstrual bleeding and frequency of dysmenorrhea.

Breast tenderness and gastric complaints were the most frequent of the common complaints due to treatment with EE/DNG. The frequency of all complaints

decreased steadily over time. Only 5.6% of subjects discontinued due to adverse reactions. No thrombophlebitic events were noticed.

Cycle control

Cycle length remained as good as unchanged at around 28 days throughout the study, while the duration of menstrual bleeding was shortened from 5.4 days at baseline to about 4.0 days during treatment. On average the intensity of bleeding was reduced. Fifty-five (13%) women reported excessive menstrual bleeding at base line, this dropped to approximately 1% by cycle 3. Further, the frequency of dysmenorrhea dropped markedly from 35% at baseline to about 10% from cycle 3 onwards as shown in table 1.

Czech Republic Study [8]

The efficacy and safety of the low dose monophasic oral contraceptive (OC) combination containing 30 μg of ethinyl estradiol (EE) and 2.0 mg of dienogest (DNG) (EE/DNG) was evaluated in a prospective, open-label, multicentre, uncontrolled, phase III trial. The trial was carried out in six hospitals by 36 investigators in the Czech Republic, and included 557 healthy women (aged 18-35 years), over 12 cycles, with a total of 6051 cycles. EE/DNG provided are reliable ovulation inhibition. The contraceptive efficacy study showed an adjusted Pearl index of 0.198 on the basis of three pregnancies occurring during 6051 cycles. EE/DNG provided good cycle control, reduced the incidence of intermenstrual bleedings, the intensity of menstrual bleeding and frequency of dysmenorrhea.

Breast tenderness and headache were the most frequent of the common complaints due to treatment with EE/DNG. The frequency of all complaints decreased steadily over time. Only 7.7% of subjects discontinued due to adverse reactions. No thrombophlebitic events were noticed.

Cycle Control

As shown in table 2, cycle length remained as good as unchanged at around 28 days throughout the study, while the duration of menstrual bleeding was shortened from 5.3 days at baseline to minimum 4.3 days during treatment. On an average the intensity of bleeding was reduced, the effect being most pronounced in those 11% of subjects who had reported excessive menstrual bleeding at baseline. Further, the frequency of dysmenorrhea (menstrual complaints) dropped markedly from 50% at baseline to about 10% from cycle 4 onwards. The majority of these subjects had reported no complaints at baseline (n = 32).

Uses

Ethinyl Estradiol + Dienogest can be used as an oral contraceptive and in the treatment of mild to moderate acne in women who seek oral contraception. In addition, combined oral contraceptives are used in heavy menstrual bleeding. They are of particular benefit for young women and adolescents who desire contraception and also require treatment for heavy menstrual bleeding.[9]

Dose

The administration of EE/DNG starts on the first

Table 1: Changes in menstruation duration, intensity and dysmenorrhea during the use of EE/DNG.

		Average Duration (days)	Intensity(%)			Dysmenorrhea(%)			
Cycle	**N**	**(mean ±SD)**	**scanty**	**normal**	**excessive**	**No**	**mild**	**Moderate**	**severe**
Baseline	**431**	**5.4**	**9.5**	**77.7**	**12.8**	**62.6**	**26.9**	**6.7**	**3.7**
1	415	4.7	33.3	63.1	3.6	84.1	8.7	7.2	0.0
2	411	4.3	45.3	52.8	1.9	88.3	8.8	2.7	0.2
3	407	4.1	50.1	48.9	1.0	89.9	7.9	2.2	0.0
4	386	4.0	45.9	53.1	1.0	91.7	4.9	3.4	0.0
5	374	4.0	49.2	49.7	1.1	93.3	4.5	2.1	0.0
6	375	3.9	50.1	49.6	0.3	92.5	5.1	2.4	0.0
7	366	3.9	42.3	56.6	1.1	85.2	12.3	2.5	0.0
8	357	4.0	42.0	57.1	0.8	84.9	12.9	2.2	0.0
9	347	4.0	45.0	54.5	0.6	84.1	12.7	3.2	0.0
10	345	3.9	40.0	59.4	0.6	84.6	12.5	2.2	0.0
11	343	3.9	43.4	55.1	1.5	84.8	11.4	3.5	0.3
12	344	3.8	41.0	59.0	0.0	84.3	11.9	3.5	0.3

Table 2 - Changes in menstruation duration, intensity and dysmenorrhea during the use of EE/DNG.

		Average Duration (days)	Intensity(%)			Dysmenorrhea(%)			
Cycle	**N**	**(mean ± SD)**	**scanty**	**normal**	**excessive**	**no**	**mild**	**Moderate**	**Severe**
Baseline	**557**	**5.3 ±1.1**	**6.8**	**82.6**	**10.6**	**48.8**	**28.9**	**16.2**	**6.8**
1	557	4.9 ±1.7	31.6	58.5	5.0	77.6	12.2	5.0	0.4
2	548	4.7 ±1.5	37.8	55.8	3.3	84.1	10.6	1.8	0.4
3	544	4.5 ±1.4	41.0	53.7	2.2	87.7	6.8	1.8	0.6
4	517	4.5 ±1.4	38.7	56.3	3.1	90.9	5.8	1.4	0.0
5	508	4.4 ±1.3	42.7	51.6	3.1	91.3	4.9	1.0	0.2
6	505	4.4 ±1.4	39.2	54.9	2.4	91.7	4.0	0.6	0.2
7	492	4.4 ±1.2	40.4	53.9	2.4	89.8	5.9	0.8	0.2
8	485	4.3 ±1.2	40.8	53.2	3.3	92.2	4.7	0.4	0.0
9	485	4.3 ±1.2	45.2	48.9	2.5	89.3	6.2	1.0	0.0
10	476	4.3 ±1.2	36.3	59.0	1.9	91.6	4.6	1.1	0.0
11	468	4.4 ±1.2	36.6	57.8	3.0	93.4	3.0	1.1	0.0
12	466	4.3 ±1.1	37.8	56.7	2.6	92.7	3.4	0.9	0.0

day of menstrual bleeding and is taken once daily for 21 days of the cycle followed by a 7-day tablet - free interval. The dose of 2 mg DNG was found to be sufficient to inhibit ovulation and the dose of 0.03mg EE ensures satisfactory cycle control while at the same time keeping estrogen related adverse events to a minimum.

Cautions

Ethinyl Estradiol + Dienogest should not be used in the presence of any of the conditions listed below:

- Presence or risk of venous thromboembolism (VTE)
- Presence or risk of arterial thromboembolism (ATE)
- Presence or history of severe hepatic disease
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Hypersensitivity to any of the ingredients

Conclusion

Ethinylestradiol/dienogest is a reliable ovulation inhibitor, with contraceptive efficacy comparable with other low-dose combined oral contraceptives. It provides good cycle control, with reduced intensity and duration of menstrual bleeding, and improves dysmenorrhoea.

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