"פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו"

1. NAME OF THE MEDICINAL PRODUCT

Tradename

ORTHO-CYCLEN®

International Non-Proprietary Name

Norgestimate and Ethinyl Estradiol [Ethinylestradiol]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Abbreviations Used: "NGM" for Norgestimate

"EE" for Ethinyl Estradiol (Ethinylestradiol)

ORTHO-CYCLEN® TABLETS

Oral Tablet	Active Ingredient Amounts	
	NGM (mg)	EE (mg)
Blue-Active	0.250	0.035

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Tablets [immediate release or prompt release, oral tablets]

Tablet Appearance:

Blue active tablets - round tablet imprinted with "C 250" on both sides.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

ORTHO-CYCLEN:

- Oral Contraceptive

4.2. Posology and Method of Administration

4.2.1. Effectiveness of Oral Contraceptive

When used perfectly, without missing any pills, the chance of becoming pregnant is less than 1% (i.e. <1 pregnancy per 100 women in their first year

of use). Typical failure rates are actually 5% in the first year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

4.2.2. Adults

To achieve the maximum contraceptive effectiveness ORTHO-CYCLEN tablets must be taken exactly as directed and in the correct order at the same time each day, e.g., at bedtime. Tablets are taken without interruption as follows:

One blue active tablet administered daily with water at the same time of the day for 21 days. After the last tablet has been taken, a period of 7 days follows, during which no tablets should be taken. During this period of no medication, bleeding can be expected, usually beginning 2 to 4 days after the last active tablet. After this break of 7 days, the next cycle of ORTHO-CYCLEN should be started, even if there is no bleeding or if bleeding has not yet ended.

For the initial cycle of therapy, treatment should commence on the first day of the menstrual cycle: one tablet daily (in the order described above) with water at the same time of the day for 21 days. If this procedure is correctly followed, TRADENAME helps to prevent pregnancy starting from the first day of intake and including the 7 days during which no tablets are taken.

Sunday Start: Take the first active tablet on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day. If Sunday is not the first day of your period, use another method of birth control as a back-up method if you have coital exposure anytime from the Sunday you start your first pack until the next Sunday (7 days).

4.2.3. Children

Safety and efficacy of ORTHO-CYCLEN tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years of age and older. Use of this product before menarche is not indicated.

4.2.4. Elderly

Use of this product is not indicated in post-menopausal women.

4.2.5. Switching from Another Hormonal Contraceptive

For a switch-over from a different combination oral contraceptive, treatment with ORTHO-CYCLEN should begin between 1 - 7 days following the last active tablet from the previous oral contraceptive cycle. In no case should more than 7 pill-free days elapse before initiating treatment with ORTHO-CYCLEN. If more than 7 days elapse between the last active pill of the previous cycle and the first active pill of the new cycle, a reliable supplementary non-hormonal contraceptive method should be used until 7 active pills have been taken without interruption. If coital exposure has occurred during such an extended pill-free interval, the possibility of fertilization should be considered.

When switching from an oral progestogen only pill, treatment with ORTHO-CYCLEN should be initiated on the first day following the last active pill. It is not necessary to use an additional non-hormonal method of contraception for the initial 7 days.

Physicians are advised to refer to prescribing information for recommendations regarding switching from another form of hormonal contraception (e.g., transdermal contraceptive system, injectables, etc.).

4.2.6. Use after Childbirth

Women who elect not to breast-feed should start oral contraceptive therapy no sooner than 3 weeks after childbirth. (See Sections 4.4.2. Thromboembolic and Other Vascular Disorders and 4.6. Pregnancy and Lactation.)

4.2.7. Use after Abortion or Miscarriage

After an abortion or miscarriage that occurs prior to 20 weeks gestation, oral contraceptives can be started immediately. An additional method of contraception is not needed. Be advised that ovulation may occur within 10 days of an abortion or miscarriage.

After an induced or spontaneous abortion that occurs at or after 20 weeks gestation, hormonal contraceptives may be started either on Day 21 post-abortion or on the first day of the first spontaneous menstruation, whichever comes first. A non-hormonal contraceptive must be used concurrently for the first 7 days of the first cycle. In exceptional cases where there are medical reasons for immediate reliable contraception, treatment with ORTHO-CYCLEN may be started within 1 week post-abortum, taking into consideration the increased risk of thromboembolic disease in the immediate

post-abortum period. (See Section 4.4.2. Thromboembolic and Other Vascular Disorders).

4.2.8. Advice in the Case of Missed Tablets

If one active tablet has been missed (no more than 24 hours should elapse between tablets), take the missed tablet as soon as it is remembered. Take the next tablet at the regular time. This means two tablets may be taken in one day.

If two active tablets are missed in week one or week two, take two tablets on the day it is remembered and two tablets the next day. Then take one tablet per day as directed until the pack is finished. In addition, a reliable supplementary non-hormonal contraceptive method should be used until active pills have been taken for 7 days without interruption.

If two active tablets are missed in week three, throw out the rest of the pill pack and start a new pack that same day. In addition, a reliable supplementary non-hormonal contraceptive method should be used until active pills have been taken for 7 days without interruption.

If three active tablets are missed anytime during the first three weeks, throw out the rest of the pack and start a new pack that same day. In addition, a reliable supplementary non-hormonal contraceptive method should be used until active pills have been taken for 7 days without interruption.

4.2.9. Breakthrough Bleeding or Spotting

In the event of breakthrough bleeding or spotting, treatment should be continued. This type of bleeding usually disappears after the third cycle, but may vary between individuals. If breakthrough bleeding persists, a healthcare professional should be consulted.

In the event of no withdrawal bleeding, treatment should be continued. If the pills have been taken correctly, the absence of such bleeding is not necessarily an indication of pregnancy. Nevertheless, the possibility of pregnancy should be ruled out.

4.2.10. In Case of Vomiting/Diarrhea

If vomiting occurs within 3 hours of pill intake, or if severe diarrhea lasting for greater than 24 hours occurs, the effectiveness of the contraception may not be adequate, and an additional non-hormonal method of contraception should be used until 7 active tablets have been taken for 7 days without

interruption. If vomiting and/or diarrhea persist, a healthcare professional should be consulted because the effectiveness of the oral contraceptive may be compromised.

4.3. Contraindications

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Known thrombophilic conditions
- Cerebral vascular or coronary artery disease
- Migraine with focal aura
- Known or suspected carcinoma of the breast
- Valvular heart disease with complications
- Persistent blood pressure values ≥ 160 mm Hg systolic or ≥100 mm Hg diastolic
- Diabetes with vascular involvement
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Acute or chronic hepatocellular disease with abnormal liver function
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy
- Hypersensitivity to any component of this product

4.4. Special Warnings and Special Precautions for Use

Oral contraceptives DO NOT protect against HIV infections (AIDS) or any other sexually transmitted disease.

Before starting, and periodically during oral contraceptive therapy, it is recommended that the patient be given a thorough physical examination. A complete medical and family history should be taken. Repeated breakthrough bleeding or unexpected vaginal bleeding requires further evaluation.

4.4.1 Smoking and Age

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including Ortho cyclen, should not be used by women who are over 35 years of age and smoke.

4.4.2. Pre-Existing Conditions

When weighing the risk/benefit of oral contraceptive use, the physician should be familiar with the following conditions which may increase the risk of complications associated with oral contraceptive use:

- Conditions which increase the risk of developing venous thrombo-embolic complications, e.g. prolonged immobilization or major surgery
- Risk factors for arterial disease, e.g. smoking, hyperlipidemia, hypertension (persistent blood pressure values ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) and obesity
- Diabetes mellitus
- Severe depression or a history of this condition

- Smoking. The risk of cardiovascular complications increases with age and the number of cigarettes smoked.

4.4.3. Thromboembolic and Other Vascular Disorders

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after the pill use is stopped.

A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 3 weeks after delivery in women who elect not to breastfeed. After an induced or spontaneous abortion that occurs at or after 20 weeks gestation, hormonal contraceptives may be started either on Day 21 post-abortion or on the first day of the first spontaneous menstruation, whichever comes first.

The relative risk of arterial thromboses (e.g. stroke, myocardial infarction) is increased by the presence of other predisposing factors such as cigarette smoking, hypertension, hyperlipidemia, obesity, diabetes, history of pre-eclamptic toxemia and increasing age. Oral contraceptives containing 50 micrograms or more of estrogen have been associated with these serious vascular complications. The risk of vascular disease may be less severe with oral contraceptive formulations containing lower dosages of estrogen and progestogen, although this has not been conclusively established.

The risk of serious cardiovascular side effects increases with age and with heavy smoking. This risk is quite marked in women over 35 years of age who smoke. Women who use oral contraceptives should be strongly advised not to smoke.

An increase in blood pressure (BP) has been reported in some women taking oral contraceptives. Studies performed with oral contraceptive formulations containing 50 micrograms or more of estrogen indicate that this increase is more likely in older oral contraceptive users and with extended duration of use. For many women, elevated blood pressure will return to normal after stopping oral contraceptives. There is no difference in the occurrence of hypertension between former and never users.

Women with hypertension [persistent systolic values of 140-159 or persistent diastolic values of 90-99 mm Hg] should have their condition under control before oral contraceptive therapy can be started. Oral contraceptive therapy should be discontinued if significant persistent elevation of blood pressure (≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic) occurs and cannot be adequately controlled. In general, women who develop hypertension during hormonal contraceptive therapy should be switched to a non-hormonal contraceptive. If other contraceptive methods are not suitable, hormonal contraceptive therapy may continue combined with antihypertensive therapy. Regular monitoring of BP throughout hormonal contraceptive therapy is recommended.

There have been clinical reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained transient, partial or complete loss of vision; onset of blurred vision or diplopia; papilledema or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

4.4.4.. Hepatobiliary Disease

At least three months should elapse after liver function tests have returned to normal following any hepatitis before administration of the oral contraceptive pill.

The incidence of both benign and malignant liver tumors (hepatic adenomas and hepatocellular carcinomas) is rare. Case-control studies have indicated that the risk of these tumors may increase in association with the use and duration of use of oral

contraceptives. Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Gallbladder disease including cholecystitis and cholelithiasis has been reported with oral contraceptive use.

4.4.5. Carcinoma of the Reproductive Organs and Breasts

In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy.

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in woman using oral contraceptives. While there are conflicting reports, most studies suggest that use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk has been reported to be related to duration of use.

A meta-analysis of 54 epidemiological studies reports that women who are currently using combined oral contraceptives or have used them in the past 10 years are at a slightly increased risk of having breast cancer diagnosed, although the additional cancers tend to be localized to the breast. It is not possible to infer from this data whether the patterns of risk observed are due to an earlier diagnosis of breast cancer in ever-users, the biological effects of hormonal contraceptives, or a combination of both factors. This meta-analysis also suggests that the age at which women discontinue the use of combined oral contraceptives is an important risk factor for breast cancer; the older the age at stopping, the more breast cancers are diagnosed. Duration of use was considered less important.

The possible increase in risk of breast cancer should be discussed with women and weighed against the benefits of combined oral contraceptives.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical neoplasia, including cervical cancer, in some populations of

women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

4.4.6. Metabolic Effects

Oral contraceptives may cause a decrease in glucose tolerance. This effect has been shown to be directly related to estrogen dose. Additionally, progestogens may increase insulin secretion and create insulin resistance, this effect varies with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, pre-diabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. Changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

4.4.7. Headache

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

4.4.8. Bleeding Irregularities

Breakthrough bleeding, spotting and/or absence of withdrawal flow may be encountered in patients on oral contraceptives, especially during the first three months of use. Non-hormonal causes should be considered and, if necessary, adequate diagnostic measures taken to rule out malignancy or pregnancy.

Some woman may experience post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

4.4.9. Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking this preparation. Chloasma is often not fully reversible.

4.5. Interactions with Other Medicinal Products and Other Forms of Interaction

4.5.1. Interactions

Changes in Contraceptive Effectiveness Associated With Co-Administration of Other Drugs:

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, she should be counseled to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:

- Some anti-epileptics (e.g. carbamazepine, eslicarbazepine acetate, felbamate, oxcarbazepine, phenytoin, rufinamide, topiramate
- (fos)aprepitant
- barbiturates
- bosentan
- colesevelam
- griseofulvin
- some (combinations of) HIV protease inhibitors (e.g nelfinavir, ritonavir, ritonavir-boosted protease inhibitors)

- modafinil
- some non-nucleoside reverse transcriptase inhibitors (e.g nevirapine)
- rifampin and rifabutin
- St. John's wort

Colesevelam: Colesevelam, given together with a combined oral hormonal contraceptive, has been shown to significantly decrease the AUC of ethinyl estradiol. No interaction was seen when the contraceptive was given 4 hours before colesevelam

Antibiotics : There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics (eg ampicillin and tetracyclines) on plasma concentrations of synthetic steroids.

Increase in Plasma Hormone Levels Associated With Co-Administered Drugs:

Some drugs and grapefruit juice may increase the plasma levels of ethinyl estradiol if co-administered. Examples include:

- acetaminophen
- ascorbic acid
- CYP3A4 inhibitors (including itraconazole, ketoconazole, voriconazole, fluconazole and grapefruit juice)
- Etoricoxib
- some HIV protease inhibitors (e.g atazanavir, indinavir)
- HMG-CoA reductase inhibitors (including atorvastatin and rosuvastatin
- Some non-nucleoside reverse transcriptase inhibitors (e.g etravirine)

Changes in Plasma Levels of Co-administered Drugs:

Combination hormonal contraceptives may also affect the pharmacokinetics of some other drugs if used concomitantly.

Examples of drugs whose plasma levels may be increased (due to CYP inhibition) include:

- cyclosporine
- omeprazole
- prednisolone
- selegiline
- theophylline
- tizanidine
- voriconazole

Examples of drugs whose plasma levels may be decreased (due to induction of glucuronidation) include:

- acetaminophen
- clofibric acid
- lamotrigine (see below)
- morphine
- salicyclic acid
- temazepam

Lamotrigine: Combined hormonal contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Physicians are advised to consult the labeling of concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations and the possible need to adjust dosages.

4.5.2. Laboratory Tests

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

- Increased prothrombin and factors II, VII, VIII, IX, X, XII and XIII; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
- Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
- Other binding proteins may be elevated in serum.
- Sex hormone-binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.
- High-density lipoprotein (HDL-C) and total cholesterol (Total-C) may be increased, low-density lipoprotein (LDL-C) may be increased or decreased, while LDL-C/HDL-C ratio may be decreased and triglycerides may be unchanged. These effects are related to the doses of estrogen and progestin, and to progestin type.
- Glucose tolerance may be decreased.
- Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

4.6. Pregnancy and Lactation

4.6.1. Use during pregnancy

TRADENAME is contraindicated during pregnancy.

Epidemiological studies indicate no increased risk of birth defects in children born to women who used oral contraceptives prior to pregnancy. The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy.

4.6.2. Use during lactation

Contraceptive steroids and/or their metabolites may be excreted in breast milk. In addition, combination hormonal contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use TRADENAME or other combination hormonal contraceptives but to use other forms of contraception until the child is fully weaned.

4.7. Effects on Ability to Drive and Use Machines

None known.

4.8. Undesirable Effects

4.8.1. Clinical Trial Data

ORTHO-CYCLEN

The safety of ORTHO-CYCLEN was evaluated in 1,891 healthy women of child-bearing potential who participated in 5 clinical trials and received at least 1 dose of ORTHO-CYCLEN for contraception. Two trials were randomized active-controlled trials and 3 were uncontrolled open-label trials. In 3 trials, subjects were followed for up to 24 cycles and in the other 2 trials, subjects were followed for up to 12 cycles.

The most frequent Adverse Drug Reactions (ADRs) reported in >5% of subjects were headache, vaginal infection, genital discharge and breast pain. Adverse Drug Reactions reported by ≥1% of ORTHO-CYCLEN-treated subjects in these trials are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥1% of ORTHO-CYCLEN-treated Subjects in 5 Clinical Trials of ORTHO-CYCLEN	
System/Organ Class	**%**
Adverse Reaction	**(N=1,891)**
Infections and Infestations	
Vaginal infection	7.5
Metabolism and Nutrition Disorders	
Fluid retention	1.0
Psychiatric Disorders	
Depression	3.4
Nervousness	3.2
Mood altered	1.4
Nervous System Disorders	
Headache	27.9
Migraine	1.5
Gastrointestinal Disorders	
Abdominal pain	4.0
Gastrointestinal pain	3.4
Flatulence	2.8
Skin and Subcutaneous Tissue Disorders	
Rash	2.2
Reproductive System and Breast Disorders	
Genital discharge	6.0
Breast pain	5.7
General Disorders and Administration Site Conditions	
Oedema	1.6
Investigations	
Weight increased	1.5

Additional ADRs reported by <1% of ORTHO-CYCLEN-treated subjects (N=1,891) in the above clinical dataset are shown in Table 2.

Table 2. Adverse Drug Reactions Reported by <1% of ORTHO-CYCLEN-treated Subjects in 5

Clinical Trials of ORTHO-CYCLEN
System/Organ Class
Adverse Reaction
Metabolism and Nutrition Disorders
Increased appetite
Decreased appetite
Weight fluctuation
Appetite disorder
Psychiatric Disorders
Libido disorder
Vascular Disorders
Hypertension
Thrombosis
Skin and Subcutaneous Tissue Disorders
Skin discolouration
Alopecia
Erythema
Reproductive System and Breast Disorders
Breast discharge
Breast enlargement
Vaginal discharge
Investigations
Weight decreased

In the above trials with ORTHO-CYCLEN, details for specific ADRs, namely nausea, vomiting, gastrointestinal disorder (reported as nausea or vomiting), dysmenorrhoea, metrorrhagia, abnormal withdrawal bleeding and amenorrhoea, were solicited or determined from bleeding pattern or cycle characteristics data on a by-treatment cycle (i.e., "by-cycle") basis, e.g., using menstrual calendars or diary cards. These ADRs are not included in Tables 1 and 2, as the incidence of each ADR was reported separately by treatment cycle only and no overall subject incidence for the whole trial was reported. In general, solicited events are associated with higher reporting rates than events spontaneously reported by subjects. In addition to the 5 clinical trials whose data were used in Tables 1 and 2, an uncontrolled, 6–cycle trial was included in the by-cycle ADR analysis (Table 3). This trial was not included in Tables 1 and 2, as it did not report overall incidences for ADR data.

By-cycle ADRs reported by ≥1% of ORTHO-CYCLEN-treated subjects in cycle 1 are shown in Table 3. With the exception of vomiting and dysmenorrhoea, the incidence of these ADRs was highest in cycle 1 and decreased over time with further treatment cycles (based on incidence data from cycles 1, 3, 6, 12, and 24). Vomiting increased in some later cycles, whereas dysmenorrhoea remained relatively stable, with a slight decrease over time.

Table 3. Adverse Drug Reactions Reported by ≥1% of ORTHO-CYCLEN-treated Subjects in Cycle 1 in 6 Clinical Trials (Except Where Specified) of ORTHO-CYCLEN

System/Organ Class		
Adverse Reaction	**Total subjects[1] (N)**	**Cycle 1(%)**
Gastrointestinal Disorders		
Nausea[2]	86	29.1
Gastrointestinal disorder[3,4]	1,639	24.6
Vomiting[2]	86	7.0
Reproductive System and Breast Disorders		
Dysmenorrhoea[5]	1,729	40.4
Metrorrhagia	10,117	26.3
Abnormal withdrawal bleeding[5]	1,667	16.9
Amenorrhoea[6]	1,783	1.6

[1]Number of subjects with available data for cycle 1.

[2]Based on data from 1 trial.

[3]Reported as nausea or vomiting.

[4]Based on data from 3 trials.

[5]Based on data from 4 trials.

[6]Based on data from 5 trials.

4.8.2. Post-Marketing Data

Adverse drug reactions first identified during post-marketing experience with NGM/EE are included in Table 4. The frequencies are provided according to the following convention:

Very common (≥1/10)

Common (≥1/100 and <1/10)

Uncommon (≥1/1,000 and <1/100)

Rare (≥1/10,000 and <1/1,000)

Very rare (<1/10,000, including isolated reports)

Not known (Cannot be estimated from the available data)

In Table 4, ADRs are presented by frequency category based on spontaneous reporting rates. The frequency category "not known" is used for ADRs for which no valid estimate of the incidence rate can be derived from clinical trials.

Table ~~7~~ 4: Adverse Drug Reactions Identified During Post-Marketing Experience with NGM/EE by Frequency Category Estimated from Spontaneous Reporting Rates	
Infections and Infestations	
Very rare	Urinary tract infection
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	
Very rare	Breast cancer, Cervical dysplasia, Benign breast neoplasm, Hepatic adenoma, Focal nodular hyperplasia, Fibroadenoma of breast, Breast cyst
Immune System Disorders	
Very rare	Hypersensitivity
Metabolism and Nutrition Disorders	
Very rare	Dyslipidaemia
Psychiatric Disorders	

Very rare	Anxiety, Insomnia
Nervous System Disorders	
Very rare	Cerebrovascular accident, Syncope, Convulsion, Paraesthesia, Dizziness
Eye Disorders	
Very rare	Retinal vascular thrombosis, Visual impairment, Dry eye, Contact lens intolerance
Ear and Labyrinth Disorders	
Very rare	Vertigo
Cardiac Disorders	
Very rare	Myocardial infarction, Tachycardia, Palpitations
Vascular Disorders	
Very rare	Arterial thromboembolism Deep vein thrombosis, Hot flush
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Pulmonary embolism, Dyspnoea
Gastrointestinal Disorders	
Very rare	Pancreatitis, Abdominal distension, Diarrhoea, Constipation
Hepatobiliary Disorders	
Very rare	Hepatitis
Skin and Subcutaneous Tissue Disorders	
Very rare	Angioedema, Erythema nodosum, Hirsutism, Night sweats, Hyperhidrosis, Photosensitivity reaction, Urticaria, Pruritus, Acne
Musculoskeletal, Connective Tissue, and Bone Disorders	
Very rare	Muscle spasms, Pain in extremity, Myalgia, Back pain
Reproductive System and Breast Disorders	
Very rare	Ovarian cyst, Suppressed lactation, Vulvovaginal dryness
General Disorders and Administration Site Conditions	
Very rare	Chest pain, Asthenic conditions
NGM/EE: norgestimate/ethinyl estradiol	

[1]Frequency category based on the higher of the 2 incidence values estimated from either clinical trials with ORTHO-CYCLEN or from clinical trials with ORTHO TRI-CYCLEN.

[2]Higher Level Term; frequency category based on incidence of most common Preferred Term within the Higher Level Term of Asthenic conditions from pooled clinical trial data, namely fatigue.

NGM/EE: norgestimate/ethinyl estradiol

4.9. Overdose

No serious ill effects have been reported following acute ingestion of large doses of oral contraceptives. Overdosage may cause nausea, vomiting and, in young girls, vaginal bleeding. There are no antidotes and treatment should be symptomatic.

4.10. [Non-Contraceptive Health Benefits

The following non-contraceptive health benefits related to the use of combination oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.

Effects on menses:

- increased menstrual cycle regularity
- decreased blood loss and decreased incidence of iron deficiency anemia
- decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:

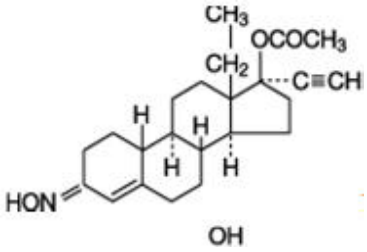
- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancies

Other effects:

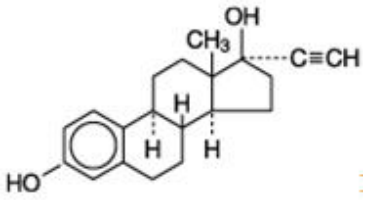
- decreased incidence of fibroadenomas and fibrocystic disease of the breast
- decreased incidence of acute pelvic inflammatory disease

- decreased incidence of endometrial cancer
- decreased incidence of ovarian cancer.]

5. PHARMACOLOGICAL PROPERTIES



Norgestimate



Ethinyl Estradiol

5.1. Pharmacodynamic Properties

ATC Code: G03AA11

Although the pharmacological actions of estrogens and progestogens which are present in all combined oral contraceptives are largely understood, the exact mechanism of their actions other than suppression of ovulation remains controversial.

TRADENAME acts through the mechanism of gonadotropin suppression by the estrogenic and progestational actions of ethinyl estradiol and norelgestromin. The primary mechanism of action is inhibition of ovulation, but alterations to the cervical mucus, the fallopian tube motility and to the endometrium may also contribute to the efficacy of the product.

Receptor and sex hormone binding globulin (SHBG) binding studies, as well as studies in animals and humans, have shown that both norgestimate (NGM) and norelgestromin, the major serum metabolite of norgestimate following oral administration, exhibits high progestational activity with minimal intrinsic

androgenicity, which illustrates the selective action of TRADENAME. Norgestimate, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in SHBG, resulting in lower levels of free testosterone in serum compared to baseline.

5.2. Pharmacokinetic Properties

Absorption: Norgestimate and ethinyl estradiol are rapidly absorbed following oral administration. Following single or multiple (three cycles) administration of TRADENAME, serum concentrations of norgestimate remain below the quantitation limit of the assay (0.1 ng/mL) due to rapid metabolism (see Metabolism below). Its metabolites, norelgestromin and norgestrel, are found in measurable concentrations in circulation, reaching maximal serum levels approximately 1.5 hours post-dose. Exposure to norelgestromin is proportional to dose following norgestimate doses of 0.180 to 0.250 mg. Ethinyl estradiol serum concentrations are measurable within 0.5 hours of dosing, reaching peak levels approximately 1.2 hours post-dose.

Distribution: Norelgestromin and norgestrel are highly bound (>97%) to serum proteins. norelgestromin is bound to albumin but not to SHBG, while norgestrel is bound primarily to SHBG and to a much lesser extent to albumin. Ethinyl estradiol is extensively bound to serum albumin.

Studies have shown that the lack of binding of norelgestromin to SHBG is unique when compared to other progestogens in oral contraceptives and plays a key role in enhancing its biological activity. In contrast, norgestrel formed from norgestimate is largely bound to SHBG, which limits its biologic activity. These findings together with the selectivity of norelgestromin for the progesterone receptor indicate that this metabolite may explain the unique clinical profile of norgestimate.

Metabolism: Norgestimate is rapidly metabolized by first-pass (intestinal and/or hepatic) mechanisms to norelgestromin (peak serum concentrations observed within 2 hours) and norgestrel, both of which are pharmacologically active progestogens. Ethinyl estradiol is metabolized to various hydroxylated metabolites and their glucuronide and sulfate conjugates.

Elimination: Both norelgestromin and norgestrel, and ethinyl estradiol are subsequently metabolized and their metabolites are eliminated by renal and fecal

pathways. Elimination half-life values at steady-state were 10 to 15 hours for ethinyl estradiol, 24.9 hours for norelgestromin and 45 hours for norgestrel. Following administration of 14C-norgestimate, 47% of the administered radioactivity was eliminated in the urine and 37% in the feces.

Steady-State Pharmacokinetics: Following administration of 0.250 mg /0.035 mg ethinyl estradiol, the daily exposure (mean AUC_{0-24h}) at steady-state, based on non-SHBG bound serum levels, was 18.1 h ng/mL for norelgestromin and 3.64 h ng/mL for norgestrel. Following oral administration of 0.150 mg levonorgestrel/0.030 mg ethinyl estradiol, mean daily exposure at steady-state, based on non-SHBG bound serum levels, was 18.9 h ng/mL for norgestrel. The exposure to norgestrel following administration of 0.250 mg /0.035 mg ethinyl estradiol, corresponds to the exposure after a levonorgestrel dose of approximately 30 micrograms in combination with ethinyl estradiol.

5.3. Preclinical Safety Data

A comprehensive set of toxicity studies have been conducted on each of the components individually and in combination. These studies include single dose studies in multiple species, repeated dose studies up to two years in the rat, seven years in the dog and ten years in the monkey, reproductive and developmental toxicity, and genetic toxicity.

Results show that the acute oral LD_{50} of norgestimate (NGM) plus ethinyl estradiol (EE) in rats is greater than 5g/kg, indicating a very low order of acute toxicity and a wide margin of safety. Repeated dose studies in general laboratory animals (rats, dogs, monkeys), at NGM + EE ratios of up to 10:1 in subchronic (3-month studies, at doses of ~ 1000 times the clinical dose) and ratios of up to 5:1 in chronic (2-year studies, at doses of ~ 100 times the clinical dose) studies, showed somewhat similar results, such as reduction of estrus cycles or menstruation, decreased uterine and ovarian weights, increased liver and pituitary weights, decreased serum cholesterol levels and erythrocytic parameters, with most of the primary treatment related effects judged to be due to an exaggerated pharmacology action of NGM + EE, or general ageing phenomenon.

In long-term studies, increased incidence of mammary neoplasms and lenticular opacities in rats (2-year study at doses up to 600 times the clinical dose) was

considered a high dose effect and probably not relevant at optimally pharmacological dose levels. In the 7-year dog study, at doses up to 25 times the clinical dose, leiomyomas (fibroids) were observed at a slightly greater incidence in the high-dose group. These tumors are the most frequent occurring spontaneous neoplasms of the reproductive tract in female dogs and are apparently due to estrogen overloading and are unlikely to occur at optimally pharmacological doses. A non-dose related lenticular opacities were also observed in the 7-year dog study. Although lenticular opacities is a normal observation in dogs, it generally has a longer latency period. Neoplasms observed in the 10-year monkey study (at doses up to 50 times the clinical dose), are single occurrences and generally in different organs, with similar spontaneous occurrences being reported in the scientific literature.

In reproduction studies, noted, dose related effects on fertility, maternal and fetal parameters, and lactation are expected responses to the pharmacological actions of this class of anti-fertility compounds and were observed at dose levels within the pharmacodynamic range. Embryolethality and skeletal variations in rats was observed with no increase in extragenital anomalies. NGM + EE is not considered a teratogen. NGM + EE, NGM and it's primary metabolite norelgestromin (NGMN), have shown no indication of any mutagenic potential.

In conclusion, the combination of norgestimate (NGM) and ethinyl estradiol (EE) in laboratory animals has shown some preclinical effects, which were observed at exposures considered sufficiently in excess of the maximum human exposure, or were the result of normal ageing process or from an exaggeration of pharmacological effects at higher than therapeutic doses indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Each tablet contains the following non active excipients: Lactose (anhydrous), Pregelatinized Starch, Magnesium Stearate and FD&C Blue No.2 Aluminum Lake

6.2. Incompatibilities

Not Applicable

6.4 Special Precautions for Storage

Do not stored above 25°C .

7. REGISTRATION HOLDER

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8. MANUFACTURER

Cilag AG, Schafhussen, Switzerland