Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

CILEST 250/35 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:
Each tablet contains 250 micrograms norgestimate and 35 micrograms ethinyl estradiol.

Excipients with known effect: Lactose monohydrate 57.065 mg
For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Blue, round, biconvex coated tablet imprinted “0 250” on one side and “35” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormonal contraception.

The decision to prescribe Cilest should take into consideration the individual woman’s current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Cilest compares with other Combined Hormonal Contraceptives (CHCs) (see sections 4.3 and 4.4).

4.2 Posology and method of administration

For oral administration.

Adults:

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.

Before starting Cilest, a thorough general medical and gynaecological examination (including the breasts and a cytological smear of the cervix) if appropriate should be carried out and the family medical history carefully noted. Disturbances of menstruation, such as oligomenorrhea and amenorrhea should be investigated prior to prescription. Disturbances of the clotting mechanisms should be ruled out if any members of the family have suffered from thromboembolic diseases (e.g. deep vein thrombosis, stroke, myocardial infarction) at a young age.

Pregnancy must be excluded ideally by a pregnancy test.

As a precaution, thorough medical examinations should be conducted at approximately six month intervals during use of the tablets (see Section 4.4).

Children:

Safety and efficacy of Cilest Tablets have only been established in women of reproductive age.

Elderly:

Not indicated in post menopausal women.

- *First cycle*

Tablet-taking from the first pack of Cilest is started on the 1st day of the menstrual cycle, i.e. the first day of menstrual bleeding. If menstruation has already begun, Cilest may be commenced up to day 5 of the menstrual period, provided additional contraceptive precautions are taken for the first 7 days of tablet taking.

One tablet is to be taken at around the same time of day on each of 21 consecutive days followed by a tablet-free interval of 7 days, during which a withdrawal bleeding occurs.

- *Subsequent cycles*

Tablet-taking from the next pack of Cilest is continued after the 7-day interval, beginning on the same day of the week as the first pack.

Changing from another oral contraceptive

- *Changing from a 21 day pill to Cilest:*

All tablets in the old pack should be finished. The first Cilest tablet is taken the next day i.e. no gap is left between taking tablets nor does the patient need to wait for her period to begin. Additional contraceptive precautions are not required. The patient will not have a period until the end of the first Cilest pack, but this is not harmful, nor does it matter if she experiences some bleeding on tablet-taking days.

- *Changing from a combined every day pill (28 day tablets) to Cilest:*

Cilest should be started after taking the last active tablet from the 'Every day Pill' pack (i.e. after taking 21 tablets). The first Cilest tablet is taken the next day, i.e. no gap is left between taking tablets nor does the patient need to wait for her period to begin. Additional contraceptive precautions are not required. Remaining tablets from the every day (ED) pack should be discarded.

The patient will not have a period until the end of the first Cilest pack, but this is not harmful, nor does it matter if she experiences some bleeding on tablet-taking days.

- *Changing from a progestogen-only pill (POP or mini pill) to Cilest:*

The first Cilest tablet should be taken on the first day of the period, even if the patient has already taken a mini pill on that day. Additional contraceptive precautions are not required. All the remaining progestogen-only pills in the mini pill pack should be discarded.

If the patient is taking a mini pill, then she may not always have a period, especially when she is breast-feeding. The first Cilest tablet should be taken on the day after stopping the mini pill. All remaining pills in the mini pill packet must be discarded. Additional contraceptive precautions must be taken for the first 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.).

- *Irregular tablet-taking*

If the patient is less than 12 hours late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is more than 12 hours late in taking any tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. tablet-taking must never be discontinued for longer than 7 days.
2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

• Week 1

The patient should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for

the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

• Week 2

The patient should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

• Week 3

The risk of reduced reliability is imminent because of the forthcoming tablet-free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.

1. The patient should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next pack must be started as soon as the current pack is finished, i.e. no gap should be left between packs. The patient is unlikely to have a withdrawal bleed until the end of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. The woman may also be advised to discontinue tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the first normal tablet-free interval, the possibility of a pregnancy should be considered.

- *Postpartum*
Women who choose not to breast-feed their newborn infant may start a new Cilest treatment on the first day of the first spontaneous menstruation or 3 weeks after delivery, whichever comes first.

- *Post-miscarriage*
Following a miscarriage at, or before, 20 weeks gestation, oral contraception can be started immediately (day 2 but no later than 5) for immediate cover. Ovulation may occur within 10 days of miscarriage.

NB: When oral contraceptives are administered in the immediate postpartum/ post-miscarriage period, the increased risk of thromboembolic disease must be considered.

- *Delaying of menstruation*
When all the tablets of the strip have been taken, a new strip can be started and tablets taken for the number of days needed. Subsequently, no tablets are taken for 7 days, followed by starting a new strip of 21 tablets with a new start day.

- *Absence of withdrawal bleeding*
If, in exceptional cases, withdrawal bleeding fails to occur, pregnancy must be ruled out before the use of Cilest is continued.

- *Procedure in the event of irregular bleeding*
Breakthrough bleeding and spotting are sometimes encountered, primarily during the first three months of use, and usually cease spontaneously. The woman, therefore, should continue to use Cilest even if irregular bleeding occurs. Should break-through bleeding persist or recur, appropriate diagnostic measures to exclude an organic cause are indicated, and may include curettage.

This also applies in the case of spotting which occurs at irregular intervals in several consecutive cycles or which occurs for the first time after long use of Cilest.

- *Gastro-intestinal upset*
Vomiting or diarrhoea may reduce the efficacy of oral contraceptives by preventing full absorption. If vomiting occurs within 3 hours of taking the tablet, or if severe diarrhoea lasts for more than 24 hours, the effectiveness of the contraception may not

be adequate, and an additional non-hormonal method of contraception should be used until 7 tablets have been taken for 7 days without interruption. If these 7 days overrun the end of a pack, the next pack should be started without a break. In this situation, a withdrawal bleed should not be expected until the end of the second pack.

If the patient does not have a withdrawal bleed during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack. Other methods of contraception should be considered if the gastro-intestinal disorder is likely to be prolonged (i.e. greater than 12 hours).

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions:

- Confirmed or suspected pregnancy

- Patients breast-feeding infants

- Presence or risk of venous thromboembolism (VTE)

● Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE])
● Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency (see section 4.4)
● Major surgery with prolonged immobilisation (see section 4.4)
● A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)

- Presence or risk of arterial thromboembolism (ATE)

● Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
● Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
● Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)
● History of migraine with focal neurological symptoms
● A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
- diabetes mellitus with vascular symptoms
- severe hypertension
- severe dyslipoproteinaemia

- Acute or chronic liver disease with abnormal liver function, jaundice or persistent pruritus during a previous pregnancy, Dubin-Johnson syndrome, Rotor syndrome, porphyria.

- Active viral hepatitis

- Severe cirrhosis of the liver

- Sickle-cell anaemia

- Current or previous known or suspected oestrogen-dependent neoplasia, e.g. previous or existing liver tumours, cancer of the breast or endometrium

- Endometrial hyperplasia

- Herpes gestationis

- Manifestation or deterioration of otosclerosis during pregnancy

- Undiagnosed vaginal bleeding

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

- Cholelithiasis

- Cholestatic jaundice of pregnancy or jaundice with prior pill use

- Systemic lupus erythematosus or a history of this condition

- Smoking more than 15 cigarettes per day in patients aged 35 years or more

Should any of the conditions appear during CHC use, the product should be stopped immediately.

Cilest is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, (see sections 4.4 and section 4.5).

4.4 Special warnings and precautions for use

Warnings

If any of the conditions/risk factors mentioned below is present, the suitability of Cilest should be discussed with the woman.

In the event of aggravation, or first appearance of any of the conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of Cilest should be discontinued.

Medical examination/consultation

Prior to the initiation or reinstitution of Cilest, a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications (see section 4.3) and warnings (see section 4.4).

It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of Cilest compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

The frequency and nature of examinations should be based upon established practice guidelines and should be adapted to the individual woman.

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

Reasons for *immediate discontinuation* of medication with Cilest:

1. Occurrence of any of the conditions listed in section 4.3.
2. Suspected or confirmed symptoms or signs of thrombophlebitis or thrombo-embolic events (e.g. unusual pains in or swelling of the legs).
3. Feeling of pain and tightness in the chest (stabbing pains on breathing or coughing for no apparent reason).
4. Occurrence for the first time, or exacerbation of migrainous headaches or development of headache with a new pattern which is recurrent, persistent or severe. Evaluation of the cause is required.
5. Sudden disturbances of vision or hearing.
6. Six weeks before elective surgery and during prolonged immobilisation e.g. after accidents, surgery.
7. Onset of jaundice, hepatitis, itching of the whole body.
8. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids.
9. Onset or worsening of epilepsy.
10. Significant rise in blood pressure.

11. Onset of severe depression.
12. Severe upper abdominal pain or liver enlargement.
13. Pregnancy.

Patients with the following conditions should only use the CHC after detailed discussion with their General Practitioner. Patients with these conditions require strict medical supervision during medication:

1. Diabetes mellitus.
2. Varicose veins.
3. Otosclerosis.
4. Multiple sclerosis.
5. Epilepsy.
6. Tetany.
7. Sydenham's chorea.
8. Renal dysfunction.
9. Family history of breast cancer or past history of breast nodules.
10. Fibrocystic disease of the breast.
11. Asthma.
12. History of clinical depression.
13. Systemic lupus erythematosus.
14. Uterine myoma.
15. Migraine.
16. Endometriosis.
17. Conditions implicated in an increased risk of developing venous thrombo-embolic complications (see 'Risk factors of VTE' below)
18. Other conditions associated with an increased risk of circulatory disease such as latent or overt cardiac failure, renal dysfunction or a history of these conditions.
19. A history of cholelithiasis.
20. Concurrent administration of rifampicin or any other product known to affect liver enzymes (see section 4.5).

Deterioration in any of the above conditions may indicate that use of the oral contraceptive should be discontinued.

Circulatory disorders

Risk of Venous Thromboembolism (VTE)

The use of any CHCs increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate (including Cilest) or norethisterone are associated with the lowest risk of VTE. The decision to use Cilest should be taken after a discussion with the woman to ensure she understands the risk of VTE with Cilest, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.**

In women who do not use a CHC and are not pregnant, about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

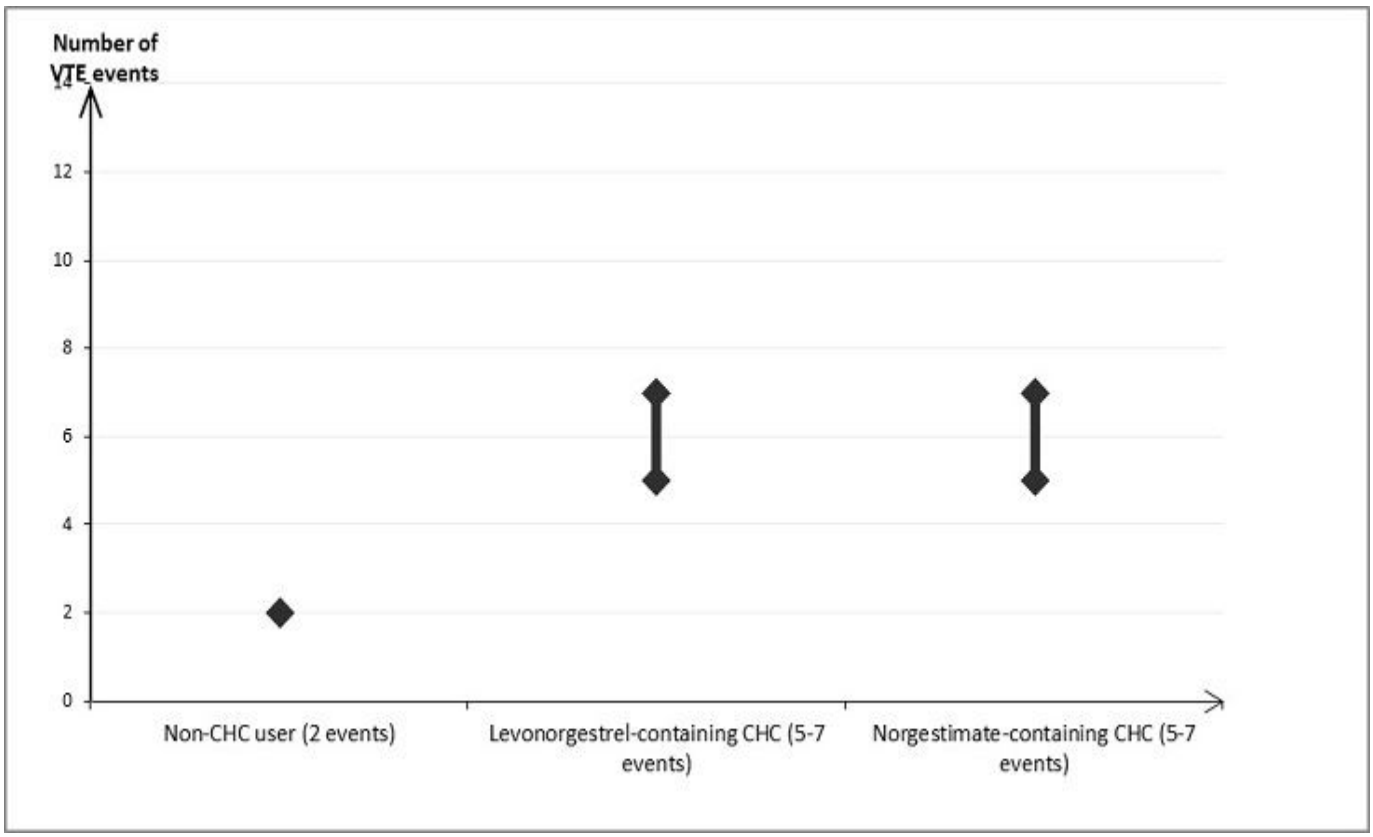
It is estimated that out of 10,000 women who use a CHC that contains levonorgestrel, about 6 will develop a VTE in a year.

Current evidence suggests that the risk of VTE with use of norgestimate-containing CHCs is similar to the risk with levonorgestrel-containing CHCs.

This number of VTEs per year is fewer than the number expected in women during pregnancy or in the postpartum period.

VTE may be fatal in 1-2% of cases.

Number of VTE events per 10,000 women in one year



Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

Risk factors for VTE

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).

Cilest is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors	In these situations it is advisable to discontinue use of the patch/Pill/ring (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Cilest has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50)	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic

	uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
Increasing age	Particularly above 35 years old

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism in pregnancy, and particularly the 6 week period of the puerperium, must be considered (for information on "Pregnancy and lactation" see section 4.6; see also graph on VTE risk).

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)
In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

- Symptoms of deep vein thrombosis (DVT) can include:
- unilateral swelling of the leg and/or foot or along a vein in the leg
- pain or tenderness in the leg which may be felt only when standing or walking
- increased warmth in the affected leg; red or discoloured skin on the leg.

- Symptoms of pulmonary embolism (PE) can include:
- sudden onset of unexplained shortness of breath or rapid breathing
- sudden coughing which may be associated with haemoptysis
- sharp chest pain
- severe light headedness or dizziness
- rapid or irregular heartbeat.

Some of these symptoms (e.g. shortness of breath, coughing) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discolouration of an extremity.

If the occlusion occurs in the eye, symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)
Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE
The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). Cilest is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	**Comment**
Increasing age	Particularly above 35 years old.
Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 35 years old who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors.
Positive family history (arterial thromboembolism ever in a sibling or	If a hereditary predisposition is suspected, the woman

parent especially at a relatively early age e.g. below 50 years old).	should be referred to a specialist for advice before deciding about any CHC use.
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

- Symptoms of a cerebrovascular accident can include:
- sudden numbness or weakness of the face, arm or leg, especially on one side of the body
- sudden trouble walking, dizziness, loss of balance or coordination
- sudden confusion, trouble speaking or understanding
- sudden trouble seeing in one or both eyes
- sudden, severe or prolonged headache with no known cause
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

- Symptoms of myocardial infarction (MI) can include:
- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone
- discomfort radiating to the back, jaw, throat, arm, stomach
- feeling of being full, having indigestion or choking
- sweating, nausea, vomiting or dizziness
- extreme weakness, anxiety, or shortness of breath
- rapid or irregular heartbeats.

Tumours

Studies in animals have indicated that administration of very high doses of oestrogens and/or progestogens will induce neoplastic tumours in some animal species.

Numerous epidemiological studies have been reported on the risk of ovarian, endometrial, cervical and breast cancer in women using combined oral contraceptives. The evidence is clear that combined oral contraceptives offer substantial protection against both ovarian and endometrial cancer.

Breast cancer

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. The excess risk gradually disappears during the course of the 10 years after cessation of CHC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent CHC users is small in relation to the overall risk of breast cancer.

It is not possible to infer from the 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 results of recent studies in human beings suggest that there is a small but statistically increased incidence of breast cancer in women who have been treated with oestrogens. The possible increase in risk of breast cancer should be discussed with women and weighed against the benefits of combined oral contraceptives.

All women, in particular those over 35 years, should have regular breast examinations while on the pill.

Cervical cancer
An increased risk of cervical cancer in long term users of combined oral contraceptives has been reported in some studies, but there continues to be controversy about the extent to which this is attributable to the confounding effects of sexual behaviour and other factors.

Hepatic adenomas
In rare cases benign and, in even rarer cases, malignant liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage have been observed after the use of hormonal substances such as those contained in Cilest. Case-control studies have indicated that the risk of these tumours may increase in association with the duration of use of oral contraceptives. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, the possibility of a liver tumour should be included in the differential diagnosis.

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.

Reduced efficacy
The efficacy of CHCs may be reduced in the event of missed tablets (section 4.2), vomiting (section 4.2) or concomitant medication (section 4.5).

Herbal preparations containing St John's Wort *(Hypericum perforatum)* should not be used while taking Cilest due to the risk of decreased plasma concentrations and reduced clinical effects of Cilest (see Section 4.5 Interactions).

ALT elevations
During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.5).

Psychiatric disorders
Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Other warnings

● An increase in blood pressure has been reported in women taking oral contraceptives. Clinically relevant increases are rare. A relationship between CHC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. 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 and where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy. Regular monitoring of blood pressure throughout hormonal contraceptive therapy is recommended. Elevated blood pressure usually returns to normal after discontinuation of oral contraceptives. Women with hypertension should have their condition under control before oral contraceptive therapy can be started.

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

● Some women may experience amenorrhoea or oligomenorrhoea after discontinuation of oral contraceptives, especially when these conditions existed prior to use. Women should be informed of this possibility.

● Oral contraceptives may cause a decrease in glucose tolerance. This effect has been shown to be directly related to oestrogen 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, cholesterol and lipoprotein levels have been reported in users of oral contraceptives. Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using CHCs.

● Crohn's disease and ulcerative colitis have been associated with CHC use.

● The following conditions have been reported to occur or deteriorate with both pregnancy and CHC use, but the evidence of an association with CHC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing-loss.

● Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Changes in Contraceptive Effectiveness Associated With Co-administration of Other Drugs:
Drugs or herbal products that induce enzymes, including CYP3A4, that metabolise contraceptive hormones, 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:
- barbiturates
- bosentan
- carbamazepine
- eslicarbazepine acetate
- felbamate
- aprepitant and fosaprepitant
- griseofulvin
- some (combinations of) HIV protease inhibitors (e.g. nelfinavir, ritonavir, ritonavir-boosted protease inhibitors)
- some HCV protease inhibitors (e.g.boceprevir, telaprevir)
- modafinil
- some non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine)
- oxcarbazepine
- phenytoin and fosphenytoin
- primidone
- rifampicin and rifabutin
- rufinamide
- St. John’s Wort
- topiramate

Management
Enzyme induction may be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks but may then be sustained for at least 4 weeks after the cessation of medicinal product therapy.

Short-term
Women receiving short-term treatment with medicinal products that induce hepatic drug metabolizing enzymes or individual active substances that induce these enzymes should temporarily use a barrier method in addition to Cilest, i.e. during the time of concomitant medicinal product administration and for 28 days after their discontinuation.

Long-term
In women on long term treatment with enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

Drugs that affect absorption
Drugs that increase gastrointestinal motility, e.g. metoclopramide, may reduce hormone absorption.

Treatment with activated charcoal will compromise absorption of steroid hormones.

Colesevelam: Colesevelam, a bile acid sequestrant, 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.

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:
- paracetamol
- ascorbic acid
- etoricoxib
- CYP3A4 inhibitors (including itraconazole, ketoconazole, voriconazole, fluconazole and grapefruit juice)
- 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:
- ciclosporin
- omeprazole
- prednisolone
- selegiline
- theophylline
- tizanidine
- voriconazole

Drugs whose plasma levels may be decreased (due to induction of glucuronidation).

Examples include:
- paracetamol
- clofibric acid
- lamotrigine (see below)
- morphine
- salicylic acid
- temazepam

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

Pharmacodynamic interactions
Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see sections 4.3 and 4.4). Therefore, Cilest users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. Cilest can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Physicians are advised to consult the labelling 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, advice regarding extra precautions and how long they must be used for.

Oral antidiabetics and insulin: The requirement for oral anti-diabetics or insulin can change as a result of the effect on glucose tolerance.

Laboratory tests

The use of oral contraceptives may influence the results of certain laboratory tests including biochemical parameters of liver, thyroid, adrenal, and renal function, plasma levels of carrier proteins and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis.

- 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 oestrogen and progestin, and to progestin type.

- Glucose tolerance may be decreased.

Laboratory staff should therefore be informed about oral contraceptive use when laboratory tests are requested.

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 Fertility, pregnancy and lactation

Pregnancy

Cilest is contraindicated during pregnancy.

If pregnancy occurs during medication with Cilest, the preparation should be withdrawn immediately.

Epidemiological studies indicate no increased risk of congenital anomalies in children born to women who used oral contraceptives prior to pregnancy. The majority of recent epidemiological studies also do not indicate a teratogenic effect, when taken inadvertently during early pregnancy.

The increased risk of VTE during the postpartum period should be considered when re-starting Cilest (see sections 4.2 and 4.4).

Breast-feeding

The use of Cilest during lactation may lead to a reduction in the volume of milk produced and to a change in its composition. Minute amounts of the active substances are excreted with the milk.

Cilest is contraindicated during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Cilest.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Description of selected adverse reactions
An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs. These are discussed in more detail in section 4.4.

The safety of Cilest was evaluated in 1,891 healthy women of child bearing potential who participated in 5 clinical trials (2 randomized active-controlled trials and 3 uncontrolled open-label trials) and received at least 1 dose of Cilest for contraception. 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.
In these studies the following ADRs were solicited or determined from bleeding pattern or cycle characteristics data and the incidence could only be determined by treatment cycle (by cycle) and not overall: nausea, gastrointestinal disorder (reported as nausea or vomiting), vomiting, dysmenorrhoea, metrorrhagia, abnormal withdrawal bleeding, amenorrhoea, and diarrhoea (diarrhoea was identified as an ADR during post-marketing review). An additional uncontrolled study (N=8,331) reported ADRs by cycle only and was only included in the incidence calculation for the by-cycle ADRs. For these by cycle ADRs, the pooled incidences for cycles 1, 3, 6, 12 and 24 were calculated and the highest cycle incidence (cycle 1 for all except vomiting and diarrhoea) presented and used to assign the ADR to a frequency category.

Based on pooled safety data from these clinical trials, the most commonly reported (i.e., ≥5% incidence) ADRs (with % incidence) were headache (27.9%), vaginal infection (7.5%), genital discharge (6.0%) and breast pain (5.7%). All by-cycle ADRs, except amenorrhoea, were very common (≥10%) in cycle 1 (dysmenorrhoea: 40.4%; nausea: 29.1%; metrorrhagia: 26.3%; gastrointestinal disorder [reported as nausea or vomiting]: 24.6%; abnormal withdrawal bleeding: 16.9% and vomiting: 7.0%). 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. The most commonly reported (≥5% incidence) ADRs identified during post marketing experience with norgestimate and ethinyl estradiol tablets (incidence from pooled clinical trial data) were diarrhoea (11.8%) and back pain* (5.4%)

*This calculated incidence value may be slightly higher than the actual incidence, as more than 1 event term reported in the same trial coded to the MedDRA preferred term of 'Back pain'. It is possible that the same subject(s) may have reported more than 1 of the event terms and may therefore be counted more than once for the Preferred Term of 'Back pain'.

The clinical trial incidence of diarrhoea was reported by cycle, therefore assignment of frequency category was based on the highest cycle incidence (cycle 12). Including the above-mentioned ADRs, Table A displays all ADRs that have been reported with the use of Cilest in clinical trials or from post marketing experiences with norgestimate and ethinyl estradiol tablets.

The displayed frequency categories use the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data).

Table A: Adverse Drug Reactions

Infections and infestations	
Common	Urinary tract infection, Vaginal infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Cervical dysplasia
Rare	Breast cyst
Frequency not known	Breast cancer, Hepatic adenoma, Benign breast neoplasm, Focal nodular hyperplasia, Fibroadenoma of breast, Hepatic tumours
Immune system disorders	
Common	Hypersensitivity
Metabolism and nutrition disorders	

Common	Fluid retention, Weight increased
Uncommon	Weight fluctuation, Weight decreased, Decreased appetite, Increased appetite
Rare	Appetite disorder
Frequency not known	Dyslipidaemia
Psychiatric disorders	
Common	Depression, Nervousness, Mood altered, Insomnia
Uncommon	Anxiety, Libido disorder
Nervous system disorders	
Very common	Headache
Common	Migraine, Dizziness
Uncommon	Syncope, Paraesthesia
Frequency not known	Cerebrovascular accident, convulsion
Eye disorders	
Uncommon	Visual impairment, Dry eye
Frequency not known	Retinal vascular thrombosis, Contact lens intolerance
Ear and labyrinth disorders	
Rare	Vertigo
Cardiac disorders	
Uncommon	Palpitations
Rare	Tachycardia
Frequency not known	Myocardial infarction
Vascular disorders	
Uncommon	Thrombosis, Hypertension, Hot flush
Rare	Venous thromboembolism, Arterial thromboembolism
Frequency not known	Deep vein thrombosis, Venous thrombosis*
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea
Frequency not known	Pulmonary embolism
Gastrointestinal disorders	
Very Common	Gastrointestinal disorder Vomiting Diarrhoea, Nausea
Common	Gastrointestinal pain, Abdominal pain, Abdominal distension, Constipation, Flatulence
Rare	Pancreatitis

Hepato-biliary disorders	
Rare	Hepatitis
Frequency not known	Cholestatic jaundice
Skin and subcutaneous tissue disorders	
Common	Acne, Rash
Uncommon	Alopecia, Hirsutism, Urticaria, Pruritus, Erythema, Skin discoloration
Rare	Hyperhidrosis, Photosensitivity reaction
Frequency not known	Angioedema, Erythema nodosum, Night sweats
Musculoskeletal and connective tissue disorders	
Common	Muscle spasms, Pain in extremity, Back pain
Uncommon	Myalgia
Reproductive system and breast disorders	
Very Common	Dysmenorrhoea, Metrorrhagia, Abnormal withdrawal bleeding
Common	Amenorrhoea, Genital discharge, Breast pain
Uncommon	Breast discharge, Galactorrhea, Breast enlargement, Ovarian cyst, Vulvovaginal dryness
Rare	Vaginal discharge
Frequency not known	Suppressed lactation
General disorders and administration site conditions	
Common	Chest pain, Oedema, Asthenic conditions

* The bundled terms for venous thrombosis include Budd Chiari Syndrome and hepatic vein thrombosis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Overdosage may cause nausea, vomiting and, in young girls, withdrawal bleeding. Serious ill effects have not been reported following large doses of oral contraceptives in children. There are no antidotes and treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

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.

Cilest 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 Cilest. 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 Cilest, 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 ^{14}C-norgestimate, 47% of the administered radioactivity was eliminated in the urine and 37% in the faeces.

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 LD50 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 neoplasm's 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 tumours 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

Core tablets:
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate
Microcrystalline cellulose

Film coating:
Hypromellose
Carnauba wax
Polyethylene glycol
Polysorbate 80
Purified water
Titanium dioxide
FD & C Blue No 2 Aluminium Lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25°C. Store blister in the outer carton.

6.5 Nature and contents of container

Carton containing 1 or 3 PVC/foil blister strips of 21 tablets each.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Janssen-Cilag Ltd
50-100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0748/029/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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