Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cilest 250/35 microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 micrograms norgestimate and 35 micrograms ethinyl estradiol.
Excipients: contains anhydrous lactose.
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Product imported from the UK:
A light blue, flat, bevel-edged tablet engraved “C” over “250” on both faces.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormonal contraception.

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 the clotting mechanisms should be ruled out if any members of the family have suffered from thrombo-embolic diseases (eg deep vein thrombosis, stroke, myocardial infarction) at a young age.
Pregnancy must be excluded ideally by a pregnancy test.
The woman should be instructed to carefully read the user leaflet and to adhere to the advice given.
As a precaution, thorough medical examinations should be conducted at approximately six month intervals during use of the tablets.

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, ie 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 styles*
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 (ie after taking 21 tablets). The first Cilest tablet is taken the next day, ie 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.

- *Postmiscarriage*
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/ postmiscarriage period, the increased risk of thrombo-embolic 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. Tablet-taking from the current pack should be continued. Additional non-hormonal methods of contraception (except the rhythm or temperature methods) should be used during the gastro-intestinal upset and for 7 days following the upset. 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 (ie greater than 12 hours).

4.3 Contraindications

1. Confirmed or suspected pregnancy
2. Patients breast feeding infants.
3. Acute or chronic liver disease with abnormal liver function, jaundice or persistent pruritus during a previous pregnancy, Dubin-Johnson syndrome, Rotor syndrome, porphyria.
4. Active viral hepatitis
5. Severe cirrhosis of the liver
6. Existing or previous arterial or venous thrombotic or embolic processes or conditions which predispose to them,

eg disorders of the clotting processes, coronary artery disease, cerebrovascular disease, valvular heart disease and atrial fibrillation. Multiple risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes and hypertension).
7. Sickle-cell anaemia.
8. Current or previous known or suspected oestrogen-dependent neoplasia, eg previous or existing liver tumours, cancer of the breast or endometrium.
9. Endometrial hyperplasia.
10. Severe diabetes mellitus with vascular changes (including retinopathy, nephropathy or neuropathy), or > 20 years' duration.
11. Disorders of lipid metabolism. (*see section 4.4, Special warnings and precautions for use*).
12. Pemphigoid gestationis.
13. Manifestation or deterioration of otosclerosis during pregnancy.
14. Undiagnosed vaginal bleeding.
15. Hypersensitivity to any of the components of Cilest.
16. Cholelithiasis.
17. Cholestatic jaundice of pregnancy or jaundice with prior pill use.
18. Systemic lupus erythematosus or a history of this condition.
19. Migraine with focal aura, or without focal aura in patients aged 35 years and over.
20. Persistent blood pressure values ≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic.
21. Smoking more than 15 cigarettes per day in patients aged 35 years or more.
22. Known thrombogenic mutations (e.g. Factor V Leiden; Prothrombin mutation; Protein S, Protein C, and Antithrombin deficiencies).

4.4 Special warnings and precautions for use

Reasons for *immediate discontinuation* of medication with Cilest.

1. Suspected or confirmed symptoms or signs of thrombophlebitis or thrombo-embolic events (eg unusual pains in or swelling of the legs).
2. Feeling of pain and tightness in the chest (stabbing pains on breathing or coughing for no apparent reason).
3. 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.
4. Sudden disturbances of vision or hearing.
5. Six weeks before elective surgery and during prolonged immobilisation eg after accidents, surgery.
6. Onset of jaundice, hepatitis, itching of the whole body.
7. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids.
8. Onset or worsening of epilepsy.
9. Significant rise in blood pressure.
10. Onset of severe depression.
11. Severe upper abdominal pain or liver enlargement.
12. Pregnancy.

Patients with the following conditions should only use the oral contraceptive pill 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, eg severe varicose veins or prolonged immobilisation or major surgery. Disorders of coagulation. Presence of any risk factor for arterial disease, such as smoking, hyperlipidemia, hypertension (persistent blood pressure values ≥ 140 mmHg systolic or ≥ 90 mm Hg diastolic) or obesity. With regards to smoking, the risk of cardiovascular complications increases with age and the number of cigarettes smoked.
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.
Oral contraceptives DO NOT protect against HIV infections (AIDS) or any other sexually transmitted disease.
In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy.

Circulatory disorders
The physician should be alert to the earliest manifestations of venous and arterial thrombo - embolic disease, ie myocardial infarction, pulmonary embolism, thrombophlebitis, stroke or retinal thrombosis.
Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen.
Should any of these occur or be suspected, Cilest should be discontinued immediately. The presence of one serious risk factor or multiple risk factors for venous or arterial disease, respectively, may also contribute to a contraindication.
Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
The physician should bear in mind the possibility of vascular accidents occurring and that there may not be full recovery from such disorders and they may be fatal.

Venous Thrombo-Embolism (VTE)
The use of combined oral contraceptives carries an increased risk of venous thrombo-embolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. The approximate occurrence of VTE in users of oral contraceptives with low oestrogen content (<50 µg ethinyl estradiol) is about 20 cases per 100,000 women-years compared to 5 to 10 cases per 100,000 women-years for non-users. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1 to 2% of these cases.
It is not known how Cilest influences the risk of VTE compared with other oral contraceptives.
The risk of venous thromboembolism increases with:
• increasing age;
• a positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use;
• obesity (body mass index over 30 kg/m^2)
• prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.
• and possibly also with superficial thrombophlebitis and varicose veins. However, there is no consensus about the possible role of these conditions in the etiology of venous thromboembolism.

Arterial thrombo-embolism
The relative risk of arterial thromboses (eg stroke, myocardial infarction) is increased by the presence of other predisposing factors such as:
a) cigarette smoking (with heavier smoking and increasing age, the risk is further increased, especially in women over 35 years of age)
b) dyslipoproteinaemia
c) hypertension
d) valvular heart disease
e) atrial fibrillation
f) obesity
g) diabetes
h) history of pre-eclamptic toxaemia
i) increasing age
j) positive family history (i.e. arterial thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.
After the age of 35 years, the physician and patients should carefully reassess the risk/benefit ratio of using combined oral contraceptives as opposed to alternative methods of contraception.

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 COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC 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. 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 COCs 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).

Other warnings
• An increase in blood pressure has been reported in women taking oral contraceptives. Clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. 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. Elevated blood pressure usually returns to normal after discontinuation of oral contraceptives.
• 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 COCs.
• Crohn's disease and ulcerative colitis have been associated with COC use.
• The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC 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 hear-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 interaction

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
• felbamate
• griseofulvin
• modafinil
• oxcarbazepine

• phenytoin
• rifampicin
• St. John's Wort
• topiramate

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors:
Significant changes (increase or decrease) in the plasma levels of the estrogen and progestin have been noted in some cases of co-administration of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

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

Women receiving short courses of enzyme inducers or broad spectrum antibiotics should take additional, non-hormonal (except rhythm or temperature method) contraceptive precautions during the time of concurrent medication and for 7 days afterwards. If these 7 days overrun the end of the 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. With rifampicin, additional contraceptive precautions should be continued for 4 weeks after treatment stops, even if only a short course was administered.

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
• CYP3A4 inhibitors (including itraconazole, ketoconazole, voriconazole and fluconazole)
• grapefruit juice
• HMG-CoA reductase inhibitors (including atorvastatin and rosuvastatin)

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
• theophylline
• 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

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.

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.

The requirement for oral antidiabetics or insulin can change as a result of the effect on glucose tolerance.

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. 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 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.

Lactation
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

The following adverse reactions have been associated with the use of norgestimate/ethinyl estradiol *(see section 4.4. Special Warnings and Precautions for Use)*:

Cilest
The evaluation of the clinical safety of Cilest was based on three Phase 3 studies conducted: a controlled 2-cell safety and efficacy comparison study (A-3437), a controlled 2-cell comparison study of coagulation effects (D83-001) and an open efficacy and safety study (C82-083). All 3 studies were two year (24 cycles) studies and cumulatively evaluated a total of 1647 women and 22,237 cycles. Information on undesirable adverse reactions from these combined studies is presented below.
Headache was the most frequently reported and only very commonly reported adverse reaction (30%).
Other adverse reactions reported in the clinical trials with a frequency below 10% are listed in the table.

ADVERSE REACTIONS REPORTED IN CLINICAL TRIALS OF CILEST			
Organ System	**Common adverse events (>1/100, <1/10)**	**Uncommon adverse events (>1/1000, <1/100)**	**Rare adverse events (>1/10000, <1/1000)**
Cardiovascular	Edema	Slight rise of blood pressure, hypertension	Myocardial infarction, deep venous thrombosis, pulmonary embolism and other embolisms
Neoplasms			Cervical cancer, breast cancer
Genital Tract	Intermenstrual		

	bleeding, spotting, amenorrhea, vaginal candidiasis		
Breast	Tenderness	Galactorrhea, pain, enlargement	
Gastro-intestinal tract	Abdominal cramps, bloating	Nausea, vomiting colitis	
Skin	Acne, rash	Alopecia, hirsuitism, chloasma	Erythema (nodosum, multiforme)
CNS	Migraine, mood changes, depression	Irritability, changes in libido	
Metabolic	Fluid retention, changes in body weight (increase or decrease)	Changes in appetite	

Listed below are adverse reactions that have been associated with the use of hormonal contraceptives:
Cardiovascular System: cerebrovascular accidents, arterial thromboembolism, myocardial infarction, hypertension
Neoplasms: benign liver tumors, malignant hepatic tumors
Hepatobiliary: intrahepatic cholestasis, cholelithiasis, cholestatic jaundice, Budd-Chiari syndrome
Genital Tract: absence of withdrawal bleeding, change in menstrual flow, increase in size of uterine fibromyoma, increase in cervical erosion and secretion, temporary infertility after discontinuation of treatment, pre-menstrual syndrome
Breast: diminution in lactation when given immediately post-partum
Skin and subcutaneous tissue: seborrhea, hypertrichosis, pemphigoid (herpes gestationis), melasma which may persist, hemorrhagic eruption, uriticaria, angiodema.
Eyes: change in corneal curvature (steepening), intolerance to contact lenses, cataracts, neuro-ocular lesions
CNS: chorea, severe headache
Metabolic: reduced glucose-tolerance
Urinary: impaired renal function, hemolytic uremic syndrome

4.9 Overdose

Overdosage may cause nausea, vomiting and withdrawal bleeding in females. 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 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 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 neoplasm's 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. Neoplasm's 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

Anhydrous lactose
Magnesium stearate
Pregelatinised starch
FD & C Blue No 2 (E132)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Store blister in outer carton to protect from light.

6.5 Nature and contents of container

Cardboard outer containing blister strips.
Pack size: 21tablets

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 PARALLEL PRODUCT AUTHORISATION HOLDER

Imbat Ltd
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North Ring Business Park
Santry
Dublin 9

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA No: 1151/108/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th July 2009

10 DATE OF REVISION OF THE TEXT

September 2010