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 ethinylestradiol.
Excipient: contains lactose anhydrous
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Product imported from the UK:
A dark 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.
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 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 (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.

- *Irregular tablet-taking*
If a patient misses one or two tablets she should take the missed tablet as soon as possible and take the next tablet at the usual time (this may mean taking two tablets at once). She should continue taking the tablets as usual thereafter, but if she is more than 12 hours late taking her tablet she should abstain from sexual intercourse or use additional, non-hormonal contraception (except rhythm or temperature method) until she has taken 7 tablets in a row. If a patient misses three or more tablets, she should take the first missed tablet as soon as
possible and take the next tablet at the usual time (this may mean taking two tablets at once). She should continue taking the tablets as usual thereafter, but should abstain from sexual intercourse or use addition, non-hormonal contraception (except rhythm or temperature method) until she has taken 7 tablets in a row.

If the tablets were missed in the third week, the patient should continue taking the tablets as usual thereafter until the pack is finished and then start the next pack immediately without waiting for a withdrawal bleed. If the tablet-free interval is avoided in this way she does not need to use emergency contraception.
If the tablets were missed in the first week (effectively extending the tablet-free interval) the patient may wish to consider the use of emergency contraception if appropriate.

- *Postpartum*
Normally, after a delivery, Cilest should be started after the first normal menstrual cycle.
If immediate reliable contraception is required for medical reasons, medication with Cilest may be initiated after day seven and before day 12 postpartum.

- *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.

- *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. Severe diabetes mellitus with vascular changes (including retinopathy, nephropathy or neuropathy), or> 20 years' duration.
10. Disorders of lipid metabolism. (See 4.4 Precautions and Warnings).
11. Pemphigoid gestationis.
12. Manifestation or deterioration of otosclerosis during pregnancy.
13. Undiagnosed vaginal bleeding.
14. Hypersensitivity to any of the components of Cilest.
15. Cholelithiasis.
16. Systemic lupus erythematosus or a history of this condition.
17. Migraine with focal aura, or without focal aura in patients aged 35 years and over.
18. Severe hypertension (persistent systolic values of 160 or persistent diastolic values 100 mm Hg).
19. Smoking more than 15 cigarettes per day in patients aged 35 years or more.

20. 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 an increased frequency of unusually severe headaches.
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. Onset or worsening of epilepsy.
8. Significant rise in blood pressure.
9. Onset of severe depression.
10. Severe upper abdominal pain or liver enlargement.
11. 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. Hypertension (persistent systolic values of 140 – 159 or persistent diastolic values of 90 – 99 mm Hg).
3. Varicose veins.
4. Otosclerosis.
5. Multiple sclerosis.
6. Epilepsy.
7. Tetany.
8. Sydenham's chorea.
9. Renal dysfunction.
10. Family history of breast cancer or past history of breast nodules.
11. Fibrocystic disease of the breast.
12. Asthma.
13. History of clinical depression.
14. Systemic lupus erythematosus.
15. Uterine myoma.
16. Migraine.
17. Endometriosis.
18. 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 or obesity. With regards to smoking, the risk of cardiovascular complications increases with age and the number of cigarettes smoked.
19. 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.
20. A history of cholelithiasis.
21. 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.

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. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per hundred thousand 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 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. Should any of these occur or be suspected, Cilest should be discontinued immediately. 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.

The relative risk of arterial thromboses (eg stroke, myocardial infarction) is increased by the presence of other predisposing factors such as:
a) cigarette smoking
b) hypercholesterolaemia
c) obesity
d) diabetes
e) history of pre-eclamptic toxaemia
f) increasing age
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.
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.

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

An increase in blood pressure has been reported in women taking oral contraceptives. Elevated blood pressure usually returns to normal after discontinuation of oral contraceptives.

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.

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.

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

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.

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.

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

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

The 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.

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

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).

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of hormonal contraceptives may be influenced by various drugs. Of potential clinical importance are drugs that cause the induction of enzymes that are responsible for the degradation of estrogens and progestins, and drugs that interrupt entero-hepatic recirculation of estrogen (e.g. certain antibiotics).

The major target for enzyme inducers is the hepatic microsomal estrogen-2-hydroxylase (cytochrome P450 3A4). Reduced contraceptive efficacy has been documented with concomitant use of hormonal contraceptives and rifampicin. Literature reports that hormonal contraceptives interact with some anti-retroviral agents, modafinil, topiramate, barbiturates, griseofulvin, phenylbutazone, phenytoin sodium, carbamazepine and bosentan. Interactions with medicines that increase clearance of sex hormones may result in breakthrough bleeding and pregnancy. The efficacy of Cilest in users who are receiving long-term treatment with a hepatic enzyme-inducing agent has not been established. Therefore, in users taking hepatic enzyme- inducing drugs, this information should be considered in choosing a contraceptive method.

A possible interaction has been suggested with hormonal contraceptives and the herbal supplement St. John's wort based on some reports of oral contraceptive users experiencing breakthrough bleeding shortly after starting St. John's wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's wort.
Some protease inhibitors and some anti-retroviral agents have been found to either increase (e.g. Indinavir) or decrease (e.g. Ritonavir) circulating levels of combination hormonal contraceptives.

Another type of interaction is the impairment of the enterohepatic recirculation of estrogens that may result in hastened elimination and impaired effectiveness. This may be due to absorption of biliary estrogen conjugates (e.g. by cholestyramine) or to insufficient cleavage of the conjuate by intestinal bacteria, the latter being observed after administration of some antibiotics (e.g. ampicillin, tetracycline).

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.

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.

4.6 Fertility, pregnancy and lactation

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

An increased risk of congenital abnormalities, including heart defects and limb defects, has been reported following the use of sex hormones including oral contraceptives in pregnancy.

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

Not applicable.

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 event (>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),

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.

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 feces.

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

5.3 Preclinical safety data

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

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

In long-term studies, increased incidence of mammary 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 its 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

Lactose (anhydrous)
Magnesium stearate
Pregelatinised starch
FD & C Blue No 2 Lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Carton containing 1PVC/foil blister strips of 21 tablets each in an overlabelled outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 465/217/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd July 2009

10 DATE OF REVISION OF THE TEXT

April 2011