Mylan Laboratories Ltd.	**CTD Module 1 (Administrative information and prescribing information)** **1.3 Labelling and Packaging**	**Version No. : 00**
Product Name: **Strength:**	**Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets** **Desogestrel 150 mcg and Ethinylestradiol 30 mcg**	

1.3.1 Summary of Product Characteristics(SmPC)

The Summary of Product Characteristics (SmPC) for Registration Dossier Meuri (Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets) is enclosed overleaf.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Name: Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets
Strength: Desogestrel 150 mcg and Ethinylestradiol 30 mcg
Pharmaceutical Form: Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active pharmaceutical ingredients: Desogestrel/Ethinylestradiol
Each of the 21 active uncoated tablets contains 150 mcg Desogestrel and 30 mcg Ethinylestradiol. Also contains Lactose.

Each of 7 green uncoated inert tablets with no active ingredient. Also contains lactose

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

3.1 General description

Active Tablets:

Round, white to off white, uncoated, biconvex tablet debossed with '142' on one side and plain on other side.

Also contains Lactose (Anhydrous Lactose): 58.115 mg.

Inert Tablets:

Round, green, uncoated, biconvex tablet debossed with '472' on one side and plain on other side.

Also contains Lactose 63.600 mg [Lactose Monohydrate (Supertab 30GR): 42.068 mg and Lactose Monohydrate (Pharmatose 200M): 21.542 mg]

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

3.2 Qualitative and quantitative composition

Active Tablets:

Each tablet contains 150 mcg Desogestrel and 30 mcg Ethinylestradiol.

Excipients: 1 uncoated tablet contains 58.115 mg of lactose anhydrous

Inert Tablets:

No Active ingredients

Excipients: 1 uncoated tablet contains 42.068 mg of lactose monohydrate (Supertab 30 GR) and 21.542 mg of lactose monohydrate (Pharmatose 200M).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception

4.2 Posology and method of administration

Route of administration: Oral use

How to take Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets

One white tablet (Active Tablet: Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablet) is to be taken for 21 consecutive days (three weeks), followed by a green tablet (Inert/Placebo Tablet: contains no active ingredients) for seven consecutive days (one week). A new pack (white tablet) will be started on the eighth day, following the completion of the green tablets. The patient will have a period while they are on the green tablet. On this regimen the patient must not go a day without taking a pill.

Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets must be taken at approximately the same time every day until the pack is empty. The patient may begin taking Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets on Day 1 of her menstrual cycle (i.e., the first day of menstrual flow) or on the first Sunday after her period begins. If the patient's period starts on Sunday, she should start that same day.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

How to start Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets

No preceding hormonal contraceptive use (in the past month)

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Tablet intake is also allowed to start on day 2-5, but during the first cycle concurrent use of a barrier method for the first 7 days of tablet intake is advisable.

- *Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring or transdermal patch)*

The woman should start taking **Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets** preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual placebo tablet interval of her previous COC. In case a vaginal ring or a transdermal patch has been used, the woman should start using **Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets** preferably on the day of removal, but at the latest when the next application would have been due.

- *Changing from a progestogen-only-method (progestogen-only-pill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)*

The woman may switch any day from the progestogen-only pills (from an implant or the IUS on the day of its removal; from an injectable when the next injection would be due) but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

- *Following first-trimester abortion*

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

- *Following delivery or second-trimester abortion*

The woman should be advised **to start** at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days. However if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

For breastfeeding women - see section 4.6.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Management of missed tablets

If the user 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 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 hypothalamus-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

- *Week 1*

The user 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 inert tablet interval, the higher the risk of a pregnancy.

- *Week 2*

The user 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 she has 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 7-day inert tablet 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, she should follow the first of these two options and use extra precautions for the next 7 days as well.

1. The user 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 blister pack must be started as soon as the current blister pack is finished, i.e., no gap should be left between packs. The user 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 blister pack. She should then have an inert tablet interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next blister pack.

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

Advice in case of gastro-intestinal disturbances

In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, a new (replacement) tablet should be taken as soon as possible. The new tablet should be taken within 12 hours of the usual time of tablet-taking if possible. If more than 12 hours elapse, the advice concerning missed tablets, under section "Management of missed tablets", is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister pack.

How to postpone a withdrawal bleed

To delay a period the woman should continue with another blister pack of **Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets** without an inert tablet interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of **Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets** is then resumed after the usual 7-day inert tablet interval.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming inert tablet interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

4.3 Contraindications

Combined oral contraceptives (COCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first during COC use, the product should be stopped immediately.

- Venous thrombosis present or in history (deep venous thrombosis, pulmonary embolism).
- Arterial thrombosis present or in history (e.g. cerebro-vascular accident, myocardial infarction) or prodromal conditions (e.g. angina pectoris and transient ischaemic attack).
- Cerebrovascular accident present or in history
- The presence of a severe or multiple risk factor(s) for arterial thrombosis:
- diabetes mellitus with vascular symptoms
- severe hypertension
- severe dyslipoproteinemia
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as APC resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.

- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding.
- History of migraine with focal neurological symptoms
- Hypersensitivity to the active substances or to any of the excipients of **Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets.**

4.4 Special warnings and precautions for use

Warnings

If one of the conditions or risk factors mentioned below is present, the benefits of COC use should be weighed against the possible risks in each individual woman and discussed with the woman, before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these risk factors, the woman should contact her physician. The physician should then decide whether COC use should be discontinued.

Circulatory disorders

The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive.

Epidemiological studies have shown that the incidence of VTE in women with no known risk factors for VTE who use low dose oestrogen (<50 µg ethinylestradiol combined oral contraceptives) ranges from about 20 cases per 100,000 woman-years (for levonorgestrel-containing COCs) to 40 cases per 100,000 women-years (for desogestrel/ gestodene-containing COC). This compares with 5 to 10 cases per 100,000 woman-years for non-users and 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Epidemiological studies have also associated the use of COCs with an increased risk for arterial (myocardial infarction, transient ischaemic attack) thromboembolism.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in contraceptive pill users. There is no consensus as to whether the occurrence of these events is associated with the use of hormonal contraceptives.

Symptoms of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident can include:

- unusual 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.

The risk for venous thromboembolic complications in COCs users increases with:

- increasing age
- a positive family history (venous thromboembolism ever in a sibling or parent at relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.
- prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Antithrombotic treatment should be considered.
- obesity (body mass index over 30 kg/m²).
- there is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The risk of arterial thromboembolic complications or of a cerebrovascular accident in COC users increases with:

- increasing age
- smoking (women over 35 years should be strongly advised not to smoke if they wish to use an COC)
- dyslipoproteinemia
- hypertension
- migraine
- obesity (body mass index over 30 kg/m2)
- a positive family history (arterial thromboembolism ever in a sibling or parent at relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use
- valvular heart disease
- atrial fibrillation

The presence of one serious risk factor or multiple risk factors for venous or arterial disease, respectively, can also constitute a contra-indication. The possibility of anticoagulant therapy should also be taken into account.COC users should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, COC use should be discontinued. Adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

The increased risk of thromboembolism in the puerperium must be considered (for information on "Pregnancy and lactation" – see section 4.6).

Other medical conditions which have been associated with adverse vascular events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle-cell disease.

An increase in frequency or severity of migraine during use of COCs (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

Tumours

An increased risk of cervical cancer in long-term users of COCs (> 5 years) has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. 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 users of COCs is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in users of COCs, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cansers diagnosed in never-users.

In rare cases, benign liver tumours, and even more rarely malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis

when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

With the use of the higher-dosed COCs (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

Other conditions

Women with hypertriglyceridaemia or a family history thereof may be at increased risk of pancreatitis when using COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. A systematic relationship between COC use and clinical hypertension has not been established. If, during the use of a COC in preexisting hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

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; gallstones; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which previously occurred during pregnancy or during previous Use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regime in diabetics using low-dose COCs (containing <0.05 mg ethinylestradiol). However, diabetic women should be carefully observed particularly in the early stage of COC use.

Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use.

Chloasma may occasionally occur, especially in women with a medical history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to sunlight or ultra-violet radiation whilst taking COCs.

Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Medical examination/consultation

Prior to the initiation or reinstitution of **Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets** 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 contra-indications (section 4.3) and warnings (section 4.4). The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

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

Reduced efficacy

The efficacy of COCs may be reduced in the event of e.g. missed tablets (section 4.2.), gastro-intestinal disturbances (section 4.2.) or concomitant medication (section 4.5.).

Reduced cycle control

With all COCs, irregular bleeding (spotting and breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about 3 cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the inert tablet interval. If the COC has been taken according to the directions described in section 4.2, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

4.5 Interaction with other medicinal products and other forms of interaction

Note: The prescribing information of concomitant medications should be consulted to identity potential interactions.

Influence of other medical products on Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets

Interactions between oral contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Hepatic metabolism

Interactions can occur with drugs that induce hepatic enzymes which can result in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin,

bosentan and HIV-medication (e.g. ritonavir, nevirapine) and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing the herbal remedy St. John's Wort (*Hypericum perforatum*). Maximal enzyme induction is generally seen in about 10 days but may then be sustained for at least 4 weeks after the cessation of drug therapy.

Interference with Enterohepatic Circulation

Contraceptive failures have also been reported with antibiotics, such as penicillins and tetracyclines. The mechanism of this effect has not been elucidated.

Management

Women on short-term treatment with any of the above-mentioned classes of medicinal products or individual active substances (hepatic enzyme-inducing medicine) besides rifampicin should temporarily use a barrier method in addition to the COC, i.e. during the time of concomitant medicinal product administration and for 7 days after their discontinuation.
For women on rifampicin a barrier method should be used in addition to the COC during the time of rifampicin administration and for 28 days after its discontinuation.
In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.
Women on treatment with antibiotics (besides rifampicin, see above) should use the barrier method until 7 days after discontinuation.
If concomitant medicinal product administration runs beyond the end of the tablets in the COC blister pack, the next COC pack should be started without the usual inert tablet interval.

Influence of Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets on other medicinal products

Oral contraceptives may affect the metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).
Laboratory analyses

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function; plasma levels of (carrier) proteins, e.g. corticosteroid-binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Fertility, Pregnancy and lactation

Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets is not indicated in pregnancy.

If pregnancy occurs during the use of **Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets** the preparation should be withdrawn immediately. Extensive epidemiological studies
have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during pregnancy.

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be recommended until the breast-feeding mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk during COC use. These amounts may affect the child.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

4.8 Undesirable effects

For serious adverse experiences in users of COCs see section 4.4.

There is an increased risk of venous thromboembolism for all women using a COC. For information on differences in risk between COCs, see Section 4.4.

Organ systems	***Very common*** **>1/10**	***Common/Uncommon*** **(more than 1/1,000 but less than 1/10)**	***Rare*** **less than 1/1000**
Infections and infestations			Vaginal candidiasis
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders		Fluid retention	
Psychiatric disorders		Libido decreased Depressed mood Mood altered	Libido increased
Nervous system disorders		Headache Dizziness Nervousness	
Eye disorders			Contact lens intolerance
Ear and labyrinth Disorders			Otosclerosis
Vascular disorders		Migraine Hypertension	Thromboembolism
Gastrointestinal disorders		Nausea Vomiting	
Skin and subcutaneous tissue disorders		Acne Rash Urticaria	Erythema nodosum Erythema multiforme Pruritus Alopecia
Reproductive system and breast disorders	Irregular bleeding	Amenorrhea Breast tenderness Breast pain Breast hypertrophy Metrorrhagia	Vaginal discharge Breast discharge
General disorders and administration site conditions	Weight increase		

The following serious adverse events have been reported in women using COCs and are discussed in section 4.4:

- Venous thromboembolic disorders;
- Arterial thromboembolic disorders;
- Hypertension;
- Liver tumours;

- Occurence or deterioriation of conditions for which an association with OC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, migraine, endometriosis, uterine myoma, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uraemic syndrome, cholestatic jaundice;
- Chloasma;
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

The frequency of diagnosis of breast cancer is very slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see sections 4.3 and 4.4.

4.9 Overdose

There has not been any experience of overdose with Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets. On the basis of general experience with combined oral contraceptives, symptoms that may possibly occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations
ATC code: G 03 AA 09

The contraceptive action of COCs is based on interaction of different factors, out of which the most important is the inhibition of ovulation and changes in the cervical secretion. Besides protection against pregnancy, COCs have several positive properties which, next to the negative properties (see Warnings, Undesirable effects), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. In the largest multicenter trial (n=23 258 cycles), the uncorrected Pearl Index is estimated at 0.1 (95% confidence interval 0.0-0.3). Furthermore, 4.5% of the women reported absence of withdrawal bleeding and 9.2% reported occurrence of irregular bleeding after 6 treatment cycles.

Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets is a COC with ethinylestradiol and the progestogen desogestrel.
Ethinylestradiol is a well known synthetic estrogen.
Desogestrel is a synthetic progestogen. After oral administration it has a strong ovulation-inhibiting activity.
With the use of the higher-dosed COCs (50µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

5.2 Pharmacokinetic properties

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Desogestrel

Absorption
After oral administration of **Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets**, desogestrel is rapidly absorbed and converted into 3-keto-desogestrel. Peak plasma levels are reached after 1.5 hours. The absolute bioavailability of 3-keto-desogestrel is 62-81%.

Distribution
3-keto-desogestrel is 95.5-99% bound to the plasma proteins, mainly albumin and SHBG. The ethinyl-oestradiol-induced increase in SHBG influences both the amount of bindings and distribution of 3-keto-deosgestrel in the plasma proteins. As a consequence the concentration of 3-keto-desogestrel rises slowly during treatment until steady state is reached within 3-13 days.

Metabolism
The phase-I metabolism of desogestrel includes cytochrom P-450 catalysed hydroxylation and subsequent dehydrogenation at C3. The active metabolite of 3-keto-desogestrel is further reduced, the degradation products are conjugated to sulphate and glucuronides. Animal studies indicate that the enterohepatic circulation has no relevance for the gestagenic activity of desogestrel.

Elimination
3-keto-desogestrel is eliminated with a mean half-life of approx. 31 hours (24-38 hours), plasma clearance varies from 5.0-9.5 l/hour. Desogestrel and its metabolites are eliminated via the urine and in the faeces, either as free steroids or conjugates. Ratio for elimination in urine or faeces is 1.5:1.

Steady-State Conditions
In steady-state conditions the serum level of 3-keto-desogestrel is elevated by two- to threefold.

Ethinylestradiol

Absorption
Ethinyl estradiol is rapidly absorbed and peak plasma levels are reached after 1.5 hours. As a consequence of presystemic conjugation and first-pass metabolism the absolute bioavailability is 60%. The area under the curve and Cmax may be expected to rise slightly over time.

Distribution
Ethinyl estradiol is 98.8% bound to the plasma proteins, almost exclusively to albumin.
Metabolism
Ethinyl estradiol undergoes presystemic conjugation both in the mucosa of the small intestine and in the liver. Hydrolysis of the direct conjugates of ethinyl estradiol with the aid of the intestinal flora gives ethinyl estradiol, which can be re-absorbed, and an enterohepatic circulation is hereby set up. The primary pathway of ethinyl estradiol metabolism is cytochrom P-450-mediated hydroxylation in which the primary metabolites are 2-OH-EE and 2-methoxy-EE. 2-OH-EE is further metabolised to chemically reactive metabolites.

Elimination
Ethinyl estradiol disappears from plasma with a half-life of approx. 29 hours (26-33 hours), plasma clearance varies from 10-30 l/hour. The conjugates of ethinyl estradiol and its metabolites are excreted via urine and faeces (ratio 1:1).

Steady-state conditions
Steady-state conditions are obtained after 3 to 4 days, when the serum drug level is approx. 30 to 40% higher than after the administration of a single dose.

5.3 Preclinical safety data

Toxicological studies have not revealed other effects than those, which can be explained, based on the hormone profile of **Desogestrel 150 mcg and Ethinylestradiol 30 mcg Tablets and Inert Tablets.**

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active Tablets:
Vitamin E
Potato starch
Povidone (E1201)
Stearic acid (E570)
Silica, colloidal anhydrous (E551)
Lactose, anhydrous

Inert Tablets:
Lactose Monohydrate (Supertab 30 GR)
Lactose Monohydrate (Pharmatose 200M)

Ferric oxide, Yellow
FD&C Blue No.1 (Lake Brilliant Blue FCF)
Polacrilin Potassium (Indion 294)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C. Protect from light.

6.5 Nature and contents of container

Clear transparent PVC/PVdC- Aluminium blister of 28 tablets, 21 Active tablets and 7 Inert tablets, per blister in packs containing 1x28 tablets. Each blister is packed in laminated film pouch.

1 such pouch to be packed in carton with one leaflet or,
3 such pouches to be packed in carton with one leaflet or,
6 such pouches to be packed in carton with one leaflet

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

7. MARKETING AUTHORISATION HOLDER:

Mylan Laboratories Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

<To be decided>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

< To be decided >

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}