IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0936/018/001
Case No: 2027670

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Pharmacia Ireland Limited

9 Riverwalk, National Digital Park, **Citywest Business Campus**, **Dublin 24**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Brevinor 500 micrograms/35 micrograms Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **07/03/2007**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Brevinor 500 micrograms/35 micrograms Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 micrograms Norethisterone and 35 micrograms Ethinylestradiol.

Excipients: also includes Lactose monohydrate 42.21 mg per tablet.

For a full list of excipeints, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Blue, round, flat tablet with beveled edges, approximately 3/16" diameter, inscribed 'Searle' on one side and 'BX' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormonal contraception

4.2 Posology and method of administration

Before starting Brevinor, a thorough general medical and gynaecological examination (including the breasts and a cytological smear of the cervix) 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 thromboembolic disease (e.g. deep vein thrombosis, stroke, myocardial infarction) at a young age.

Pregnancy must be excluded ideally by a pregnancy test.

As a precaution, through examinations should be conducted at approximately six-month intervals during use of tablets.

- First Cycle

Tablet-taking form the first pack of Brevinor is started on the 1st day of the menstrual cycle, i.e. the first day of the menstrual bleeding. Additional contraceptive precautions should be taken for the first 7 days of the first pack. Patients unable to start taking Brevinor tablets on the first day of the menstrual cycle may start treatment on any day up to and including the 5th day of the menstrual cycle. It is also recommended that another method of contraception is used for the first 7 days of tablet-taking in those patients delaying therapy up to Day 5. 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 Brevinor is continued after the 7-day interval, beginning on the same day of the

week as the first pack.

- Changing from another oral contraceptive

The first tablet of Brevinor should be taken on the first day of bleeding that occurs after the intake of the last active tablet of the patient's previous oral contraceptive.

- Irregular tablet taking

If the woman forgets to take a Brevinor tablet then it must be taken within 12 hours of the usual time for taking it. If a missed tablet is not taken within 12 hours then it should be taken when remembered and the remaining tablets taken as usual with extra non-hormonal contraceptive measures (except rhythm or temperature method) used for the next 7 days. If these seven days extend beyond the end of the pack then the next pack of tablets should be commenced at once with no tablet-free interval. 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 excluded before resuming with the next pack.

- Postpartum

Normally, after a delivery, Brevinor should be started after the first normal menstrual cycle.

If immediate reliable contraception is required for medial reasons, medication with Brevinor should be initiated after Day 7 and before Day 12 postpartum.

- Postmiscarriage

Following a miscarriage oral contraception can be started immediately (Day 2 but no later than Day 5) for immediate cover.

When oral contraceptives are administered in the immediate postpartum/postmiscarriage period, the increased risk of thromboembolic 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 Brevinor 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 Brevinor even if irregular bleeding occurs. Should break-through bleeding persist or recur, appropriate diagnostic measures to exclude an organic cause should be taken.

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 Brevinor.

- Gastro-intestinal upset

Vomiting or diarrhoea may reduce the efficacy or 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 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. Other methods of contraception should be considered if the gastro-intestinal disorder(s) is likely to be prolonged.

4.3 Contraindications

1. Confirmed or suspected pregnancy and in nursing mothers.

2. Acute or chronic liver disease, jaundice or persistent pruritis during a previous pregnancy, Dubin-Johnson syndrome and Rotor syndrome.

3. Presence or history of thrombophlebitis or thromboembolic disorders, cardiovascular disease, myocardial infarction, coronary artery disease or congenital hyperlipidema.

4. Sickle-cell anaemia.

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

6. Severe diabetes mellitus with vascular changes.

7. Disorders of lipid metabolism (See 4.4 Special warnings and precautions for use).

8. Pemphigoid gestationis.

9. Deterioration of otosclerosis during pregnancy.

10. Undiagnosed vaginal bleeding.

11. Hypersensitivity to any of the components of Brevinor.

4.4 Special warnings and precautions for use

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 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 100,000 pregnanies. VTE is fatal in 1-2 % of cases.

It is not known how Brevinor influences the risk of VTE compared with other combined oral contraceptives.

Reasons for <u>immediate discontinuation</u> of medication with Brevinor:

1. Suspected or confirmed symptoms or signs of thrombophlebitis or thromboembolic events (e.g. unusual pains in or swelling of the legs).

2. Pulmonary embolic disease and/or a 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 or migrainous headaches or an increased frequency or unusually severe headaches.

4. Sudden disturbances of vision or hearing or other perceptual disorders.

5. Four weeks before elective surgery and during immobilisation e.g. after accidents, surgery. It would be reasonable to resume Brevinor two weeks after surgery providing the woman is ambulant. However, every woman should be considered individually with regard to the nature of the operation, the extent of immobilisation, the presence of

additional risk factors and the chance of unwanted conception.

6. Onset of jaundice, hepatitis, itching of the whole body.
7. Increases in epileptic seizures.
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 detailing discussion with their General Practitioner. Patients with these conditions require strict medical supervision during medication.

1. Diabetes mellitus or impaired carbohydrate tolerance.
2. Hypertension.
3. Varicose veins.
4. Otosclerosis.
5. Multiple sclerosis.
6. Epilepsy.
7. Porphyria.
8. Tetany.
9. Sydenham’s chorea.
10. Cardiac or renal dysfunction.
11. Family history of breast cancer or past history of breast nodules.
12. Fibrocystic disease of the breast.
13. Asthma.
14. History of clinical depression.
15. Systemic lupus erythematosus.
16. Uterine myoma.
17. Migraine.
18. Endometriosis.

19. Women who wear contact lenses.

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

According to the present state of knowledge, an association between the use of hormonal contraceptives and an increased risk of venous and arterial thromboembolic disease such as myocardial infarction, pulmonary embolism, thrombophlebitis, stroke or retinal thrombosis, cannot be ruled out. The physician should be alert to the earliest manifestations of these disorders. Should any of these occur or be suspected Brevinor should be discontinued immediately.

The relative risk of arterial thromboses (e.g. 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.

Changes in serum triglycerides, cholesterol and lipoprotein levels have been reported in users of oral contraceptives.

Oral contraceptives may cause a decrease in glucose tolerance.

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.

Women with a history of oligomenorrhea or secondary amenorrhoea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrhoeic after discontinuation of oral contraceptives. Women with these pre-existing problems should be advised of this possibility and encouraged to use other contraceptive methods.

Numerous epidemiological studies have been reported on the risks 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.

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 Brevinor. If severe upper abdominal complaints, liver enlargement or signs or intra-abdominal haemorrhage occur, the possibility of a liver tumour should be included in the differential diagnosis.

Earlier studies reported an increased risk of surgically confirmed gallbladder disease in users of oestrogens and oral contraceptives. However, more recent studies have shown that the relative risk of the developing gallbladder disease may be minimal.

Six months should elapse after the regression of viral hepatitis before administration of the oral contraceptive pill.

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

The results of recent studies in human beings suggest that there is a small but statistically increased incidence of endometrial carcinoma and of breast cancer in women who have been treated with oestrogens. All women in particular those over 35 years should have regular breast examinations while on the pill.

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

Hepatic enzyme inducers such as barbiturates, primidone, hydantoins, phenylbutazone, rifampicin, carbamazepine and griseofulvin can impair the efficacy of Brevinor. For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be used. The use of ampicillin and other antibiotics may also reduce the efficacy of Brevinor, possibly by altering the intestinal flora and individual pregnancies have been reported. St. John's Wort should not be taken concomitantly with Brevinor as it could lead to a loss of contraceptive effect.

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 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 or 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 Pregnancy and lactation

If pregnancy occurs during medication with Brevinor, 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. It is advisable to discontinue Brevinor three months before a planned pregnancy.

The use of Brevinor 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. As the effect of Brevinor has not been determind in breast-fed infants, it is recommended that patients who are breast feeding should not take this product.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

There is an increased risk of venous thromboembolism for all women using a combined oral contraceptive.

Cases of headaches (including migranes), gastric upsets including dyspepsia, nausea and vomiting, breast tenderness, changes in body weight, fluid retention, bloating, thrombophlebitis, changes in libido, breakthrough bleeding, failure of withdrawal bleeding to occur, depressive moods, candidiasis, rash, urticaria, pruritis, erythema nodosum, erythema multiforme, acne, hirsutism and alopecia can occur.

In predisposed women, use of Brevinor can sometimes cause chloasma, which is exacerbated by exposure to sunlight.

Individual cases of poor tolerance of contact lenses have been reported with use of oral contraceptives. Contact lens wearers who develop changes in lens tolerance should be assessed by an ophthalmologist.

Refer to Section 4.4 Special warnings and special precautions for use for additional information.

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. In general, treatment of overdose is not necessary ; however, treatment may be symptomatic, if appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The mode of action of Brevinor is similar to that of other progestogen/oestrogen oral contraceptives and includes the inhibition of ovulation, the thickening of cervical mucus so as to constitute a barrier to sperm and the rendering of the endometrium unreceptive to implantation. Such activity is exerted through a combined effect on one or more of the following: hypothalamus, anterior pituitary, ovary, endometrium and cervical mucus.

5.2 Pharmacokinetic properties

Following oral administration, the absolute bioavailability of norethisterone is about 65%. The time to peak plasma concentration ranges from 0.5 to 4 hours, being more delayed as the dose increases. There is extensive first-pass metabolism. In the plasma, about 80% is bound to sex hormones binding globulin and albumin. The elimination half-life ia about 5-14 hours.

After oral administration the absolute bioavailability of ethinyloestradiol is about 40%. Peak plasma concentration is reached in 1 to 2 hours. Protein binding, primarily to albumin, is about 98%. There is extensive first-pass metabolism and extensive enterohepatic circulation. The elimination half-life is 6 to 20 hours.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn Starch
Povidone
Magnesium Stearate
Lactose monohydrate
FD & C Blue No. 2 (E132)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

5 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC/Foil laminate blister enclosed in a cardboard outer. Each pack contains 21 tablets.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmacia Ireland Limited
9 Riverwalk
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8 MARKETING AUTHORISATION NUMBER

PA 936/18/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 07 March 2007

10 DATE OF REVISION OF THE TEXT

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