Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Microval 30 microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 micrograms of levonorgestrel.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Coated tablet.
White, shiny, odourless tablets with a smooth surface.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormonal contraception

4.2 Posology and method of administration

How to take Microval

To achieve maximum contraceptive effectiveness, Microval must be taken exactly as directed. One tablet is taken every day at the same time, preferably after the evening meal or at bedtime so that the interval between tablets is always about 24 hours. The tablets should be taken with no interruption, whether bleeding occurs or not. Each subsequent pack is started on the day after the previous pack is finished. Contraceptive efficacy may be reduced if a tablet is taken more than 3 hours late.

During the first cycle additional non-hormonal contraceptive precautions should be taken for the first 14 days.

How to start Microval:

No preceding hormonal contraceptive use (in the past month):

The tablets are started on the first day of menstruation and taken daily without interruption for as long as contraception is desired. They should be taken at the same time each day, preferably after the evening meal or at bedtime so that the interval between tablets is always about 24 hours. Protection may be reduced when the interval increases beyond 27 hours.

During the first cycle additional contraceptive non-hormonal precautions should be taken for the first 14 days.

Changing from another type of progestogen-only method (implant, injection):

Tablet-taking should start on the day of an implant removal or, if using an injection, the day the next injection would be due. In addition, a non-hormonal back-up method of birth control should be used for the first 14 days.

Changing from a combined oral contraceptive (COC):

Women who change from a combined oral contraceptive to Microval should stop taking the previous product, leave seven clear days and take the first Microval tablet on the eighth day, then continue to take 1 tablet daily. Additional non-hormonal contraceptive precautions should be taken until the fourteenth tablet has been taken.

Post-partum women who are breast feeding:

In women who are breast-feeding tablet taking may start six weeks after delivery. A non-hormonal back-up method of birth control should be used for the last 14 days.

Following miscarriage, or for postpartum women who are not breast-feeding:

Tablet-taking may start immediately. A non-hormonal back-up method of birth control should be used for the first 14 days.

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

Irregular spotting or bleeding may occur with a proportion of women initially but menstrual regularity is usually re-established after the first few cycles. Those patients whose menstrual patterns do not become reasonably regular after three to four cycles or who have prolonged bleeding or amenorrhea lasting for two months should be instructed to return for advice.

Management of missed tablets.

If a tablet is not taken at the usual time it should be taken as soon as possible and the next tablet taken at the usual time. If the interval between tablets is more than 27 hours protection may be impaired. The patient should take one tablet as soon as she remembers and thereafter one tablet daily as before but should use additional contraceptive measures until the tablets have been taken regularly for 14 days. If a tablet is missed, the patient should take 1 tablet daily as before but should use additional non-hormonal contraceptive measures until the tablets have been taken regularly for 14 days. In addition, if three or more tablets have been missed, the possibility of pregnancy should be considered before tablet-taking is resumed.

Advice in case of gastro-intestinal upset

If vomiting occurs shortly after a tablet has been taken contraceptive protection can be maintained by taking another tablet, provided that it is taken within three hours of the normal time. The last tablet in the pack may be used for this purpose. If repeated vomiting or diarrhoea endanger absorption additional non-hormonal contraceptive precautions should be used for 14 days after the symptoms have disappeared.

Other methods of contraception should be considered if the gastro-intestinal disorder is likely to be prolonged.

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 Microval 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 prolonged use of Microval.

Advice in Case of Missed Withdrawal Bleeding:

If one withdrawal bleed is missed and Microval has not been taken according to directions, or if two consecutive withdrawal bleeds are missed, tablet-taking should be discontinued until the possibility of pregnancy is excluded. In addition, a non-hormonal back-up method of contraception should be used.

4.3 Contraindications

1. Confirmed or suspected pregnancy.

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

3. Existing or previous arterial or venous thrombotic or embolic processes or conditions which predispose to them e.g. disorders of the clotting processes, coronary artery disease, cerebrovascular disease, valvular heart disease and atrial fibrillation.

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

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

6. Undiagnosed vaginal bleeding.

7. Hypersensitivity to any of the components of Microval.

4.4 Special warnings and precautions for use

Reasons for immediate discontinuation of medication with Microval:

1 Suspected or confirmed symptoms or signs of thrombophlebitis or thromboembolic events (e.g. 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 or other perceptual disorders.

5 Six weeks before elective surgery and during immobilisation e.g. after accidents, surgery.

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 detailed discussion with their General Practitioner. Patients with these conditions require strict medical supervision during medication:

1 Diabetes mellitus

2 Hypertension

3 Varicose veins

4 Multiple sclerosis

5 Epilepsy

6 Porphyria

7 Tetany

8 Syndenham'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

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

The following warnings and precautions should also be considered:

· Assessment of women prior to starting oral contraceptives (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for this product. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and, if judged appropriate by the clinician, breast, abdominal and pelvic examination including cervical cytology.

· Ectopic pregnancies occur more frequently in women on progesterone oral contraceptive pills. The possibility of an ectopic pregnancy should therefore be considered in women who become pregnant or complain of lower abdominal pain while on progestogen-only pills (POPs).

· If follicular development occurs, atresia of the follicle is sometimes delayed and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally, these enlarged follicles are asymptomatic and disappear spontaneously. However, in some cases they may be associated with mild abdominal pain. Rarely ovarian torsion or follicular rupture may occur, requiring surgical intervention.

· A meta-analysis of 54 epidemiological studies reported that there is a slightly increased relative risk of having breast cancer diagnosed in women who are currently using oral contraceptives (OC). The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs or a combination of both. The additional breast cancers diagnosed in current users of OCs or in women who have used OCs in the last ten years are more likely to be localised to the breast than those in women who never used OCs.

Breast cancer is rare among women under 40 years of age whether or not they take OCs. Whilst the background risk increases with age, the excess number of breast cancer diagnoses in current and recent progestogen-only pill (POP) users is small in relation to the overall risk of breast cancer, possibly of similar magnitude to that associated with combined OCs. However, for POPs, the evidence is based on much smaller populations of users and so is less conclusive than that for combined OCs.

The most important risk factor for breast cancer in POP users is the age women discontinue the POP; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping POP use, such that by 10 years there appears to be no excess.

The evidence suggests that compared with never-users, among 10,000 women who use POPs for up to 5 years but stop by age 20, there would be much less than 1 extra case of breast cancer diagnosed up to 10 years afterwards. For those stopping by age 30 after 5 years use of the POP, there would be an estimated 2-3 extra cases (additional to the 44 cases of breast cancer per 10,000 women in this age group never exposed to oral contraceptives). For those stopping by age 40 after 5 years use, there would be an estimated 10 extra cases diagnosed up to 10 years afterwards (additional to the 160 cases of breast cancer per 10,000 never-exposed women in this age group).

It is important to inform patients that users of all contraceptive pills appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of oral contraceptives, but that this has to be weighed against the known benefits.

· Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings are attributable to the confounding effects of sexual behaviour and other factors. There are insufficient data to determine if the use of POPs increases the risk of developing these conditions. In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

· Irregular or intermenstrual bleeding may occur in women using POPs. However, if such bleeding is suggestive of infection, malignancy, pregnancy or other conditions, such causes should be evaluated. If one menstrual period is missed and the POP has not been taken according to directions, or if two consecutive menstrual periods are missed, the possibility of pregnancy should be evaluated.

· According to the present state of knowledge, and an increased risk of venous and arterial thromboembolic disease such as myocardial infarction, pulmonary embolism, thrombophlebitis, stroke or retinal thrombosis has been associated with the use of COCs. There have been reports of these conditions coincident with the use of POPs although the data are limited and do not suggest an increased risk of these conditions. The possibility of thrombosis should, however, be considered and the physician should be alert to the earliest manifestations of these disorders. Should any of these occur or be suspected, Microval should be discontinued immediately. Care should be used when prescribing POPs to women predisposed to thromboembolic disorders (e.g. a history of thromboembolic events, thrombophilia, cardiovascular disease; women who are obese or experience prolonged immobilisation).

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

· 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. Although some studies have shown that diabetic women taking POPs do not generally experience changes in insulin requirements, the possibility of potential clinical effects should be considered.

· 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.

· Women with a history of oral contraception related cholestasis or women with cholestasis during pregnancy are more likely to have this condition with oral contraceptive use. If these patients receive a POP they should be carefully monitored and, if the condition recurs, POP use should be discontinued.

Progestogens may be poorly metabolised in patients with impaired liver function. Such patients should be carefully observed if POPs are prescribed. Six months should elapse after the registration of viral hepatitis before administration of the oral contraceptive pill.

· 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 Microval. 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.

· The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of POPs and evaluation of the cause.
Women with migraine (particularly migraine with aura) who take POPs may be at increased risk of stroke.

· The limited available data do not indicate a significant delay in the return of the woman's normal ovulation and fertility following discontinuation of POPs.

· Patients should be counselled that this product does not protect against HIV (AIDS) infection or other sexually transmitted diseases.

· Diarrhoea may increase gastrointestinal motility and reduce hormone absorption.

· Herbal preparations containing St John's wort (*Hypericum perforatum*) should not be used while taking Microval because of the risk of decreased plasma concentrations which could result in reduced clinical effects of Microval (see 4.5 Interactions).

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

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be observed in prescribing oral contraceptives for patients taking other drugs as several interactions have been reported. The effectiveness of POPs may be reduced by hepatic enzyme-inducing drugs such as phenytoin, carbamazapine, barbiturates, rifampicin, and some protease inhibitors.

It is recommended that additional non-hormonal contraception be used during concomitant use of POPs and substances that may affect the contraceptive efficacy of POPs or following the discontinuation of substances that have led to induction of hepatic microsomal enzymes. It may take several weeks until enzyme induction has subsided, depending on dosage, duration of use, and rate of elimination of the inducing substance. For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be considered.

Steroids affect drug metabolism and the therapeutic or toxic effects of other drugs may be modified. Interactions have been reported between oral contraceptives and tricyclic antidepressants, anticoagulants and corticosteroids.

Other mechanisms which may affect the contraceptive efficacy of POPs include any substance that reduces gastrointestinal transit time.

The herbal preparation St John's wort (Hypericum perforatum) should not be taken at the same time as this medicine because of the potential loss of contraceptive effect. Breakthrough bleeding and unintended pregnancies have been reported as a result of induction of drug metabolising enzymes by St John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort.

The prescribing information of concomitant medications should be consulted to identify potential interactions.

Laboratory parameters:

Sex hormone-binding globulin (SHBG) concentrations may be decreased.

Some tests of thyroid function may be altered, particularly total thyroxine (T4) which may be decreased.

4.6 Fertility, pregnancy and lactation

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

Although studies with oral contraceptives do not suggest a teratogenic effect the risk cannot be completely excluded. Microval should be discontinued if pregnancy is suspected.

Numerous studies have evaluated POP use in breast-feeding women and their infants. Small amounts of progestogens and/or their metabolites have been identified in the milk of nursing mothers. Very rarely, adverse effects on the child have been reported, including jaundice.

4.7 Effects on ability to drive and use machines

Microval should not affect the ability to drive or use machinery.

4.8 Undesirable effects

The following effects have been reported:

Reproductive system and breast disorders:
Amenorrhoea: breakthrough bleeding/spotting; change in menstrual flow; breast pain, enlargement, tenderness, secretion; galactorrhoea; ectopic pregnancy; delayed follicular atresia; vaginal discharge; vaginitis

Metabolism and nutrition disorders:
Glucose intolerance; changes in appetite (increase or decrease); exacerbation of poryphryia

Psychiatric disorders:
Depressed moods; decreased libido

Nervous system disorders:
Headache, including severe headache; dizziness; nervousness

Eye disorders
Retinal vascular thrombosis

Valcular disorders:
Pulmonary embolism; venous thromboembolism, including deep vein thrombosis and thrombophlebitis: retinal vascular thrombosis; myocardial infarction; stroke

Gastrointestinal disorders:
Abdominal pain; abdominal cramps; abdominal distension; nausea; vomiting

Skin and subcutaneous tissue and bone disorders:
Acne; alopecia; hirsutism; chloasma/melasma that may persist; rash; candidiasis; pruritis; erythema nodosum; erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:
Leg cramps/pain

Immune system disorders:
Anaphylactic/anaphylactoid reactions, including urticaria, throat tightness, and facial oedema

General disorders and administration site reactions:
Fatigue; oedema; fluid retention

Investigations:
Increased AST, ALT, bilirubin; decreased HDL; increased blood pressure; changes in body weight.
A common feature of all Microval oral contraceptives is that they produce an initial irregularity of the bleeding pattern which tends to decrease with time. The patient should be informed that her menstrual pattern is likely to alter prior to commencing treatment. If pregnancy and organic causes for the irregular bleeding are ruled out, there is no reason to discontinue treatment. Refer to section 4.4 ‘Special warnings and precautions for use’ for additional information.

4.9 Overdose

Overdosage may cause nausea, vomiting, breast tenderness, dizziness, somnolence and withdrawal bleeding in females. Treatment of overdose, if necessary, is directed to the symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Hormonal Contraceptives for Systemic Use; Progestogens ATC code: G03A C03

Levonorgestrel appears to exert its contraceptive effects by various methods. These include:

1) An effect on cervical mucous by which sperm do not penetrate through it easily and which appears to affect the capacitation phenomenon.

2) Inhibition of ovulation in some cases.

3) Changes in endometrial structure affecting implantation.

5.2 Pharmacokinetic properties

Absorption
Levonorgestrel is rapidly and completely absorbed from the gastrointestinal tract, with an absolute bioavailability of approximately 100%. Peak levonorgestrel serum concentration is reached in about 1-2 hours.

Distribution
Levonorgestrel is extensively bound to SHBG and albumin and only 1-2% of the total serum drug concentration is present as free steroid.

Metabolism
The most important metabolic pathway occurs in the reduction of the Δ 4-3-oxo group and hydroxylation at position 2α, 1β and 16β, followed by conjugation. Most of the metabolites that circulate in the blood are sulphates of 3α, 5 β-tetrahydro-levonorgestrel, while excretion occurs predominantly in the form of glucuronides. Some of the parent levonorgestrel also circulates as 17 β-sulphate. Metabolic clearance rates may differ among individuals by several-fold and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

Excretion
The elimination half-life for levonorgestrel is approximately 36±13 hours at steady state. Levonorgestrel and its metabolites are primarily excreted in the urine (40% to 68%) and about 16% to 48% are excreted in faeces.

5.3 Preclinical safety data

No preclinical safety data other than those described elsewhere in this document are considered relevant to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Starch
Povidone 25
Talc
Magnesium stearate

Tablet coat:
Sucrose
Povidone K90

Calcium carbonate
Macrogol 6000
Carnauba wax
White beeswax

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25^0C. Store in the original package.

6.5 Nature and contents of container

Primary container
Polyvinylchloride (PVC)/Aluminium foil blister pack.

Secondary container
Cardboard carton.

Presentation
Each blister pack contains 35 tablets.
Carton contains 1 blister.

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

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 822/67/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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