Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Femicept 150 / 30 Coated Tablets /
Levest 150 / 30 Coated Tablets

(levonorgestrel, ethinylestradiol)

UK/H/1865/001/DC

UK licence numbers: PL 32821/0002

Famy Care Europe Ltd

LAY SUMMARY

On 4th December 2009, the MHRA granted Famy Care Europe Ltd a Marketing Authorisation (licence) for the medicinal product Femicept 150 / 30 Coated Tablets / Levest 150 / 30 Coated Tablets (PL 32821/0002, UK/H/1865/001/DC). This is a prescription-only medicine (POM).

Femicept / Levest 150 / 30 Coated Tablets are a combined oral contraceptive and belong to a group of products often referred to as 'the Pill'. Femicept / Levest contains two hormones: estrogen (ethinylestradiol) and progestogen (levonorgestrel). These hormones prevent you from getting pregnant, just as your natural hormones would prevent you from conceiving again when you are already pregnant.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Femicept 150 / 30 Coated Tablets / Levest 150 / 30 Coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information About Initial Procedure

Product Name	Femicept 150 / 30 Coated Tablets / Levest 150 / 30 Coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Ethinylestradiol, levonorgestrel
Form	Coated tablets
Strength	150 mcg levonorgestrel 30 mcg ethinylestradiol
MA Holder	Famy Care Europe Ltd. One Wood Street, London, EC2V 7WS, United Kingdom
RMS	UK
CMS	Belgium, Denmark, Finland, Germany, Hungary, Netherlands, Norway, Poland
Procedure Number	UK/H/1865/001/DC
Timetable	Day 210 – 15th November 2009

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Femicept 150/30 Coated Tablets

Levest 150/30 Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 150 micrograms Levonorgestrel and 30 micrograms Ethinylestradiol.

Excipients: 1 coated tablet contains 58.170 mg of lactose monohydrate and 12.030 mg of sucrose

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Coated tablet

White, circular, biconvex, coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

4.2 Posology and method of administration

How to use Femicept/ Levest
One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet free interval, during which time a withdrawal bleed usually occurs.

The bleeding usually starts within 2 to 3 days after the last tablet and may not end before the next pack is started.

How to start the use of Femicept/ Levest tablets

- no preceding hormonal contraceptive use (in the past month), tablet-taking is started on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2–5 is allowed but in that case an additional barrier method is recommended for the first 7 days of the first cycle

- Changing from another combined hormonal contraceptive (COC, vaginal ring, transdermal patch)
  The use of Femicept/ Levest tablets is preferably started on the day after the last active tablet of the previous COC (or after removal of the ring or patch), but at the latest on the day following the usual tablet-free (ring-free, patch-free) break or the last placebo tablet of the previous hormonal contraceptive.

- Changing from a progestogen-only method (oral pill, injection, implant) or intrauterine system (IUS)
  The woman can switch to Femicept/ Levest tablets any day from the minipill (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 use an additional barrier method for the first 7 days of tablet-taking.

- Following first-trimester abortion
  The use of the tablets can start immediately. In such a case, no other contraceptive measures are needed.

- Following delivery or second-trimester abortion
  For breast-feeding, see Section 4.6 Pregnancy and Lactation.

The use of the tablets is started 21 to 28 days after delivery or second-trimester abortion. When starting later, an additional barrier method must be used for the first 7 days of tablet-taking. If the woman has already had sexual intercourse, pregnancy must be excluded before the actual start of COC use or the woman has to wait for her next menstrual period.

Missed tablets

Femicept/ Levest contains a very low dose of both hormones, and, as a consequence, the contraceptive efficacy margin is small, if a pill is missed. If the woman 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 take the next tablets at the usual time.

If she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced. The following two basic rules apply in cases where tablets have been missed:

1. Tablet-taking must never be discontinued for longer than 7 days.

2. Adequate suppression of the hypothalamic-pituitary-ovarian axis requires 7 days of uninterrupted tablet-taking.

Accordingly, the following advice can be given for daily practice:

Week 1
The woman 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 the next tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If the woman has had sexual intercourse in the 7 days before missing the tablet, the possibility of a pregnancy must be considered. The more tablets have been missed and the closer they are to the regular tablet-free break, the higher the risk of pregnancy.

Week 2
The woman 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 the next 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. If she has not taken the tablets correctly or has missed more than one tablet, she should be advised to use extra contraceptive precautions for the next 7 days.

Week 3
The risk of reduced contraceptive reliability is imminent because of the forthcoming tablet-free break of 7 days. However, reduced contraceptive protection can still be prevented by adjusting the dosage. By adhering to the following advice, there is no need to use extra contraceptive precautions, provided that all the tablets have been taken correctly in the 7 days preceding the first missed tablet. If this is not the case, the woman should follow the first of these two options and use extra contraceptive precautions for the next 7 days as well.

1. The woman 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 the next tablets at her usual time. The next pack is started as soon as the current pack is finished, i.e. there is no tablet-free break. There will probably be no withdrawal bleed until the end of the second pack, but the woman may experience spotting or breakthrough bleeding on tablet-taking days.

2. It is also possible to stop taking tablets from the current pack. The woman must then have a tablet-free break of 7 days, including the days she missed tablets, and then continue with the next pack.

If the woman misses several tablets and has no withdrawal bleed during the first normal tablet-free break, the possibility of a pregnancy must be considered.

Advice in case of gastrointestinal disturbances

In case of severe gastrointestinal symptoms, absorption of the active ingredients may not be complete and additional contraceptive measures should be taken.

If vomiting or severe diarrhoea occurs within 3 to 4 hours after taking a tablet, the woman should apply the advice given for missed tablets. If the woman does not want to change her normal tablet schedule, she has to take the extra tablets from another pack.

How to change the starting day of a period or to delay a period

To delay a period the woman should start a new pack immediately after finishing the current pack without any break. Periods can be delayed as long as wished, but no later than till the end of the second pack. During this time the woman may experience breakthrough bleeding or spotting. Regular intake of Femicept/ Levest tablets is then resumed after the usual 7-day tablet-free break.

If the woman wants to change the starting day or her periods to another day of the week, she can be advised to shorten her next tablet-free break by as many days as she likes. The shorter the break, the higher the risk that there will be no withdrawal bleed and that the woman will experience breakthrough bleeding and spotting during the second 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 time 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. 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 dyslipoproteinaemia
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as APC resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- History of migraine with focal neurological symptoms
- Pancreatitis or history of such a condition, if associated with severe hypertriglyceridaemia
- Severe hepatic disease, current or previous, 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
- Amenorrhoea of unknown cause
- Hypersensitivity to the active substances levonorgestrel, ethinylestradiol or to any of the excipients in Femicept/ Levest tablets

4.4 Special warnings and precautions for use

Warnings:
If any of the conditions/risk factors mentioned below is present, the benefits of COC use should be weighed against the possible risks for 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 conditions or risk factors, the woman should contact her physician. The physician should then decide on whether COC use should be discontinued.

Vascular disorders

Epidemiological studies have shown that the incidence of VTE in users of oral contraceptives with low oestrogen content (<50 µg ethinylestradiol) ranges from about 20 to 40 cases per 100,000 women-years, but this risk estimate varies according to the progestogen. This compares with 5 to 10 cases per 100,000 women-years for non-users. 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. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases.

The overall absolute risk (incidence) of VTE for levonorgestrel containing combined oral contraceptives with 30 µg ethinylestradiol is approximately 20 cases per 100,000 women-years of use.

Epidemiological studies have also associated the use of combined COCs with an increased risk for myocardial infarction, transient ischaemic attack and for stroke.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal 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
- first occurrence or worsening of migraine
- 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.

Occurrence of one or more of these symptoms may be a reason for immediate discontinuation of Femicept/ Levest.

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 immobilisation, 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 if the pills have not been discontinued in advance.
- 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 thrombo-embolic 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)
- dyslipoproteinaemia
- hypertension
- migraine, especially migraine with focal neurological symptoms
- 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 (see Section 4.6 Pregnancy and Lactation).

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

An increase in frequency or severity of migraine during COC use (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 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 of 54 epidemiological studies showed that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. This excess risk gradually disappears during the course of 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. 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 COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in everusers tend to be less advanced clinically than the cancers 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 intraabdominal 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.

- Other conditions

Women with hypertriglyceridaemia, or a family history thereof, may be at an 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 during 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 erythaematosus, haemolytic uremic syndrome, Sydenham's chorea, herpes gestationis, otosclerosis-related hearing loss depressive mood.

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 the liver function values return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which previously occurred during pregnancy or previous use of sex steroids necessitates 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 regimen in diabetics using low-dose COCs. However, diabetic women should be carefully monitored, 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 history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

Medical examination/consultation

Prior to the initiation or reinstitution of Femicept/ Levest 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 (see section 4.3 Contraindications) and warnings (see section 4.4 Special Warnings and special precautions for use). 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) and other sexually transmissible diseases.

Reduced efficacy

The efficacy of COCs may be reduced, in the event of missed tablets vomiting or diarrhoea or concomitant medication.

Reduced cycle control

With all COCs, irregular bleeding (spotting or 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 three cycles. In users of Femicept/ Levest, any bleeding (spotting and/or break-through bleeding) was reported by more than 50% during the first 6 months of use.

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 tablet-free 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.

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

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

- Interactions

Interactions between COCs and other drugs may impair the contraceptive efficacy and/or lead to breakthrough bleeding.

Reduced absorption: Drugs that increase gastrointestinal motility, e.g. Metoclopramide, may reduce hormone absorption.

Hepatic metabolism: Interactions can occur with drugs that induce hepatic microsomal enzymes, resulting in increased clearance of sex hormones. These drugs include hydantoin derivatives (e.g. phenytoin), barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin. Herbal preparation containing St. John's wort should not be taken concomitantly with Femicept/ Levest tablets as this could potentially lead to a loss of contraceptive efficacy. Breakthrough bleedings and unintended pregnancies have been reported. The enzyme inducing effect may persist for 2 weeks after cessation of treatment with St. John's wort.

Also HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, have been reported to potentially affect hepatic metabolism.

Enterohepatic circulation: Some clinical reports suggest that the enterohepatic circulation of estrogens may decrease when certain antibiotic agents (e.g. penicillins, tetracyclines) are given at the same time, which may reduce the ethinylestradiol concentration in serum.

Women on treatment with any of these drugs should temporarily use a barrier method or another method of contraception in addition to the COC. With liver enzyme inducing drugs, the barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use a barrier method during the use of the antibiotics and until 7 days after their discontinuation. If the drug therapy runs beyond the end of the tablets in the COC pack, the next COC pack should be started right after the previous one without the usual tablet-free interval.

Oral contraceptives may interfere with the metabolism of other drugs. Increased plasma concentrations of cyclosporin have been reported with concomitant administration of OCs. COCs have been shown to induce metabolism of lamotrigine resulting in sub-therapeutic plasma concentrations of lamotrigine.

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

- Laboratory tests

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 blood coagulation and fibrinolysis. The changes generally remain within the normal laboratory range.

4.6 Pregnancy and lactation

Femicept/ Levest is not indicated in pregnancy.

If the woman becomes pregnant while using Femicept/ Levest tablets, further intake must be stopped immediately.

However, most epidemiological studies have revealed neither an increased risk of birth defects in children born to women taking contraceptive pills before pregnancy, nor any teratogenic effects at unintentional intake of contraceptive pills in early pregnancy.

Lactation may be influenced by contraceptive pills since they may reduce the amount of breast milk and change its composition. Thus, the use of combined oral contraceptives should generally not be recommended until the nursing mother has weaned her child off breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted in breast milk. These amounts may affect the infant.

4.7 Effects on ability to drive and use machines

Femicept/ Levest has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly adverse drug reaction in COC users is headache (17 – 24 % of women).

Other adverse effects that have been reported in users of combined hormonal contraceptives including Femicept/ Levest are:

Organ system	Common (>1/100)	Uncommon (>1/1000 and <1/100)	Rare (< 1/1000),
Eye disorders			contact lens intolerance
Gastrointestinal disorders	nausea, abdominal pain	vomiting, diarrhoea	
Immune system disorders			hypersensitivity
Investigations	weight increased		weight decreased
Metabolism and nutrition disorders		fluid retention	
Nervous system disorders	headache	migraine	
Psychiatric disorders	depressed mood, mood altered	libido decreased	libido increased
Reproductive system and breast disorders	breast tenderness, breast pain	breast enlargement	breast discharge, vaginal discharge
Skin and subcutaneous tissue disorders	rash	urticaria	erythema nodosum, erythema multiforme

*The most appropriate MedDRA term (version 7.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

The following serious adverse events have been reported in women using COCs, which are discussed in section 4.4 Special warning and precautions for use:

- Venous thromboembolic disorders;
- Arterial thromboembolic disorders;
- Hypertension;
- Liver tumours;
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, migraine, endometriosis, uterine myoma, porphyria, systemic lupus erythaematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice;

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 Contraindications and 4.4 Special warning and precautions for use.

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

4.9 Overdose

There have been no reports of serious adverse effects from overdose. Symptoms that may be caused by overdose are nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and the treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogen and estrogens, fixed combinations, ATC Code: G03AA07

The contraceptive effects of COCs are based on the interaction of various factors. The most important of these factors are the inhibition of ovulation and changes in the cervical mucosa

Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year. The failure rate may increase when pills are missed or taken incorrectly.

The contraceptive effect of COCs is based on the interaction of various factors. The most important of these factors are the inhibition of ovulation and changes in the cervical mucus.

Clinical trials have been performed in 2498 women aged 18 to 40 years. The overall Pearl Index calculated from these trials was 0.69 (95% confidence interval 0.30 – 1.36) based on 15,026 treatment cycles.

5.2 Pharmacokinetic properties

- Levonorgestrel

Absorption
Orally administered levonorgestrel is absorbed rapidly and completely. Peak serum concentrations of about 2.3 ng/ml are reached about 1.3 hours after taking a Femicept/ Levest tablet. The bioavailability is nearly 100%.

Distribution
Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only 1.1% of the total serum drug concentrations are present as free steroid, approximately 65% are specifically bound to SHBG and approximately 35% are non-specifically bound to albumin. The ethinylestradiol-induced increase in the SHBG concentration influences the relative distribution of levonorgestrel into different protein fractions. Induction of the binding protein causes an increase in the SHBG-bound fraction and a decrease in the albumin-bound fraction. The apparent volume of distribution of levonorgestrel is 129 l after a single dose.

Metabolism
Levonorgestrel is completely metabolized by the typical pathways of steroid metabolism. The metabolic clearance rate from serum is approximately 1.0 ml/min/kg.

Elimination
Levonorgestrel levels in serum decrease in two phases. The terminal phase is characterized by a half-life of approximately 25 hours. Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary (feces) ratio of about 1:1. The half-life of metabolite excretion is about 1 day.

Steady state
During the continuous use of Femicept/ Levest tablets, serum levonorgestrel levels increase about threefold reaching steady-state conditions during the second half of the treatment cycle. Levonorgestrel pharmacokinetics are influenced by the SHBG levels in serum, which are increased 1.5–1.6-fold during the use of estradiol. Therefore, the clearance rate from serum and the volume of distribution are slightly reduced at steady state (0.7 ml/min/kg and about 100 l).

- Ethinylestradiol

Absorption
Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of about 50 pg/ml are reached within 1–2 hours after taking a Femicept tablet. During absorption and first-pass hepatic metabolism ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 45% (interindividual variation about 20–65%).

Distribution
Ethinylestradiol is highly (approximately 98%) but non-specifically bound to serum albumin, and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of ethinylestradiol is 2.8–8.6 l/kg.

Metabolism
Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation, forming various hydroxylated and methylated metabolites that are present as free metabolites or as glucuronide or sulfate conjugates in serum. The metabolic clearance rate from serum is 2.3–7 ml/min/kg.

Elimination
Ethinylestradiol levels in serum decrease in two phases characterized by half-lives of about 1 hour and 10–20 hours, respectively.

Ethinylestradiol is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of 4:6, and the half-life is about 1 day.

Steady state
Ethinylestradiol concentration in serum increases about twofold after continuous use of Femicept / Levest tablets. Due to the variable half-life of the terminal phase in serum clearance and the daily administration, steady-state conditions are reached within about a week.

5.3 Preclinical safety data

Preclinical studies (general toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction) have not revealed other effects than those which can be explained based on the known hormone profile of ethinyl estradiol and levonorgestrel.

However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose Monohydrate
Maize Starch
Talc
Povidone K-25
Magnesium Stearate

Coating:
Sucrose
Talc
Calcium carbonate
Povidone K-90
Glycerol
Macrogol 6000
Titanium dioxide (E171)
Carnauba Wax

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25^0 C

6.5 Nature and contents of container

Tablets are packed in PVC/PVDC/Aluminium blisters

Presentation:

Pack sizes:

21 coated tablets (1 blister of 21)

63 coated tablets (3 blisters of 21)

126 coated tablets (6 blisters of 21)

273 coated tablets (13 blisters of 21)

6.6 Special precautions for disposal

Keep out of reach and sight of children

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

7 MARKETING AUTHORISATION HOLDER

Famy Care Europe Ltd.
One Wood Street
London, EC2V 7WS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 32821/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/12/2009

10 DATE OF REVISION OF THE TEXT

04/12/2009

Module 3

Product Information Leaflet

The leaflet is identical for Levest 150/30 Coated Tablets apart from the product name

Femicept 150/30 Coated Tablets

Levonorgestrel 150 micrograms & Ethinylestradiol 30 micrograms

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT FEMICEPT IS AND WHAT IT IS USED FOR

Femicept coated tablets are a combined oral contraceptive and belongs to a group of products often referred to as "the Pill". Femicept contains two hormones: estrogen (Ethinylestradiol) and progestogen (Levonorgestrel). These hormones prevent you from getting pregnant, just as your natural hormones would prevent you from conceiving again when you are already pregnant.

2. BEFORE YOU USE FEMICEPT

General notes

Before you can begin taking Femicept your doctor will ask you some questions about your personal health and that of your close relatives. The doctor will also measure your blood pressure and depending upon your personal situation, may also carry out some other tests.

In this leaflet, several situations are described where you should stop using Femicept, or where the reliability of Femicept may be decreased. In such situations you should either not have intercourse or you should take extra non-hormonal contraceptive precautions, e.g., use a condom, or another barrier method. Do not use rhythm or temperature methods. These methods can be unreliable because Femicept alters the monthly changes of the cervical mucus.

Femicept, like other hormonal contraceptives, does not protect against HIV infection (AIDS) or any other sexually transmitted disease.

Do not take Femicept

- If you are allergic (hypersensitive) to any of the ingredients of Femicept.
- If you have (or have had in the past) a blood clot (thrombosis) in a blood vessel of the leg, lung (embolus) or other organs.
- If you have (or have had in the past) a heart attack or stroke.
- If you have (or have had in the past) a disease that can be a predictor of a heart attack (for example, angina pectoris, which causes severe pain in the chest) or of a stroke (for example, a transient slight stroke with no residual effects).
- If you have a disease that may increase the risk of a thrombosis in the arteries. This applies to the following diseases:
  - Diabetes mellitus with damaged blood vessels
  - Very high blood pressure
  - A very high level of fat in the blood (cholesterol or triglycerides)
- If you have a disturbance of blood clotting (for example, protein C deficiency).
- If you have (had) a certain form of migraine (with so-called focal neurological symptoms).
- If you have (had) an inflammation of the pancreas (pancreatitis).
- If you have or have had in the past a liver disease and your liver function is still not normal.
- If you have or have had a tumour in the liver.
- If you have (had) or if you are suspected to having breast cancer or cancer of the genital organs.
- If you have any unexplained bleeding from the vagina.
- If you have absence of menstrual period and the cause is unknown.

Take special care with Femicept

In some situations you need to take special care while using Femicept or any other combined hormonal contraceptive, and it may be necessary that you are regularly checked by your doctor. If any of the following conditions applies to you, you must inform your doctor before starting to use Femicept. Also is any of the following conditions develops or worsens during the use of Femicept you must consult your doctor.

- If a close relative has or has had breast cancer.
- If you have a disease of the liver or the gallbladder.
- If you have diabetes.
- If you have depression.
- If you have Crohn's disease or ulcerative colitis (inflammatory bowel disease).

- If you have HUS (haemolytic uremic syndrome; a blood disease that causes kidney damage).
- If you have epilepsy (see "Taking other medicines").
- If you have SLE (systemic lupus erythaematosus; a disease of the immune system).
- If you have a disease that first appeared during pregnancy or earlier use of sex hormones (for Example, hearing loss, porphyria (a disease of the blood), gestational herpes (skin rash with vesicles during pregnancy), Sydenham's chorea (a disease of the nerves in which sudden movements of the body occur).
- If you have or have ever had chloasma (golden brown pigment patches, so called "pregnancy patches", especially on the face). If this is the case, avoid direct exposure to sunlight or ultraviolet light.
- If you have hereditary angioedema, products containing estrogens may induce or worsen symptoms of angioedema. You should see your doctor immediately if you experience symptoms of angioedema such as swollen face, tongue and/or pharynx and/or difficulty swallowing or hives together with difficulty breathing.
- If a pre-existing high blood pressure condition worsens.
- If a pre-existing high level of fat in blood worsens.

Femicept and thrombosis

Venous thrombosis

The use of any combination pill, including Femicept, increases a woman's risk of developing a venous thrombosis (formation of a blood clot in vessels) compared with a woman who does not take any (contraceptive) pill.

The risk of venous thrombosis in users of combined pills increases:

- With increasing age.
- If you are overweight.
- If one of your close relatives has had a blood clot (thrombosis) in the leg, lung, or other organ at a young age.
- If you must have an operation (surgery), any prolonged period of immobilization, or if you have had a serious accident. It is important to tell your doctor in advance that you are using Femicept as the treatment may have to be stopped. Your doctor will tell you when to start again. This is usually about two weeks after you are back on your feet.

Arterial thrombosis

The use of combination pills has been connected with an increase of the risk of arterial thrombosis (obstruction of an artery), for example, in the blood vessels of the heart (heart attack) or the brain (stroke).

The risk of arterial thrombosis in users of combined pills increases:

- With increasing age.
- **If you smoke you are strongly advised to stop smoking when you use Femicept, especially if you are older than 35 years.**
- If you have an increased fat content in your blood (cholesterol or triglycerides).
- If you have high blood pressure.
- If you have migraine.
- If you have a problem with your heart (valve disorder, a disturbance of the heart rhythm).

Stop taking Femicept and tell your doctor immediately if after taking Femicept you notice possible signs of thrombosis, such as

- any unusual, severe or long-lasting headache or worsening of migraine.
- partial or complete blindness or double vision.
- sudden pain and/or swelling in one of your legs.
- sudden breathlessness.
- sudden cough without an obvious cause.
- sudden severe pain in the chest which may reach the left arm.
- difficulty in speaking or inability to speak.
- weakness, strange feeling, or numbness in any part of the body.
- a feeling of dizziness or spinning.
- collapse with or without focal seizure.
- motor disturbances.
- sudden severe abdominal pain.

Femicept and cancer

Breast cancer has been observed slightly more often in women using combined pills, but it is not known whether this is caused by the treatment. For example it may be that more tumours are detected in women on combined pills because they are examined by their doctor more often. The occurrence of breast tumours becomes gradually less after stopping the combination hormonal contraceptives. It is important to regularly check your breasts and you should contact your doctor if you feel any lump.

In rare cases, benign liver tumours, and in even fewer cases malignant liver tumours have been reported in pill users. Contact your doctor if you have unusual severe abdominal pain.

Bleeding between periods

During the first few months that you are taking Femicept, you may have unexpected bleeding (bleeding outside the gap week). If this bleeding lasts longer than a few months, or if it begins after some months, your doctor must investigate the cause.

What you must do if no bleeding occurs in the gap week
If you have taken all the tablets correctly, have not had vomiting or severe diarrhoea and you have not taken any other medicines, it is highly unlikely that you are pregnant.

If the expected bleeding does not happen twice in succession, you may be pregnant. Contact your doctor immediately. Do not start the next strip until you are sure that you are not pregnant.

Taking other medicines
Always tell the doctor, who prescribes Femicept, which medicines or herbal products you are already using. Also tell any other doctor or dentist who prescribes another medicine (or the dispensing pharmacist) that you are using Femicept. They can tell you if you need to take additional contraceptive precautions (for example condoms) and if so, for how long.

- Some medicines can make Femicept less effective in preventing pregnancy, or can cause unexpected bleeding. They include medicines used for the treatment of epilepsy (e.g., primidone, phenytoin, barbiturates, carbamazepine, oxcarbamazepine, topiramate, felbamate) and tuberculosis (e.g. rifampicin), or HIV infections (ritonavir, nevirapine) or other infectious diseases (griseofulvin, penicillin, tetracycline), medicines that increase the motility of your intestines (metoclopramide), and the herbal remedy St. John's wort.
- Femicept may influence the effect of other medicines, e.g. medicines containing cyclosporin, or the anti-epileptic lamotrigine (this could lead to an increased frequency of seizures).

Ask you doctor or pharmacist for advice before taking any medicine.

Effect on laboratory tests
If you need a blood test, tell your doctor or the laboratory staff that you are taking the pill, because oral contraceptives can affect the results of some tests.

Pregnancy
If you become pregnant while taking Femicept you must stop immediately and contact your doctor.

Ask your doctor or pharmacist for advice before taking any medicine.

Breast feeding
Use of Femicept is generally not advisable when a woman is breast feeding. If you want to take the pill while you are breast-feeding you should contact your doctor.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Femicept does not have any known effect on your ability to drive or use machines.

Important information about some of the ingredients of Femicept
Femicept contains **lactose** and **sucrose**. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE FEMICEPT

Always take Femicept exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Take one tablet of Femicept every day, if necessary with a small amount of water. You may take the tablets with or without food, but you should take the tablets every day around the same time.

The strip contains 21 tablets. Next to each tablet is printed the day of the week that it should be taken. If, for example you start on a Wednesday, take a tablet with "WED" next to it. Follow the direction of the arrow on the strip until all 21 tablets have been taken.

Then take no tablets for 7 days. In the course of these 7 tablet-free days (otherwise called a stop or gap week) bleeding should begin. This so-called "withdrawal bleeding" usually starts on the 2nd or 3rd day of the gap week.

On the 8th day after the last Femicept tablet (that is, after the 7-day gap week), start the following strip, even if the bleeding has not stopped. This means that you should start the following strip on the same day of the week and that the withdrawal bleed should occur on the same days each month.

If you use Femicept in this manner, you are also protected against pregnancy during the 7 days that you are not taking a tablet.

Starting the first pack of Femicept

- If you have not used a contraceptive with hormones in the previous month.

Begin with Femicept on the first day of the cycle (that is the first day of your menstruation). If you start Femicept on the first day of your menstruation you are immediately protected against pregnancy. You may also begin on day 2-5 of the cycle, but then you must use extra protective measures (for example, a condom) for the first 7 days.

- Changing from another combined hormonal contraceptive, or combined contraceptive, vaginal ring or patch.

You can start Femicept preferably on the day after the last active tablet (the last tablet containing the active substance) of your previous pill, but at the latest on the day after the tablet-free days of your previous pill finish (or after the last inactive tablet of your previous pill). When changing from a combined contraceptive vaginal ring or patch, follow the advice of your doctor.

- Changing from a progestogen-only-method (progestogen-only pill, injection, implant or a progestogen-releasing IUD).

You may switch any day from the progestogen-only pill (from an implant or the IUD on the day of its removal, from an injectable when the next injection would be due) but in all of these cases you must use extra protective measures (for example, a condom) for the first 7 days of tablet-taking.

- After a miscarriage.

Follow the advice of your doctor.

- After having a baby.

After having a baby, you can start Femicept between 21 and 28 days later. If you start later than day 28, you must use a so-called barrier method (for example, a condom) during the first seven days of Femicept use.
If, after having a baby, you have had intercourse before starting Femicept (again), you must first be sure that you are not pregnant or you must wait until the next menstrual bleed.

Let your doctor advice you in case you are not sure when to start.

- If you are breastfeeding and want to start Femicept after having a baby.

Read the section on "Breast feeding".

If you take more Femicept than you should
There are no reports of serious harmful results of taking too many Femicept tablets.
If you take several tablets at once then you may have symptoms of nausea or vomiting. Young girls may have bleeding from the vagina.
If you have taken too many Femicept tablets, or you discover that a child has taken some, ask your doctor or pharmacist for advice.

If you forget to take Femicept
If you are **less than 12 hours late** in taking your pill, the protection from pregnancy is not reduced. Take the tablet as soon as you remember, and further pills again at the usual time.

If you are **more than 12 hours** late taking a tablet, the protection from pregnancy may be reduced. The greater the number of tablets that you have forgotten, the greater is the risk that the protection from pregnancy is reduced.

The risk of incomplete protection against pregnancy is greatest if you forget a tablet at the beginning or the end of the strip. Therefore, you should adhere to the following rules:

More than one tablet forgotten in this strip
Contact your doctor.

One tablet forgotten in week 1
Take the forgotten tablet as soon as you remember, even if that means that you have to take two tablets at the same time. Take the tablets again at the usual time and use **extra precautions** for the next 7 days, for example, a condom. If you have had intercourse in the week before the oversight or you have forgotten to start a new strip after the tablet-free period, you must realize that there is a risk of pregnancy. In that case, contact your doctor.

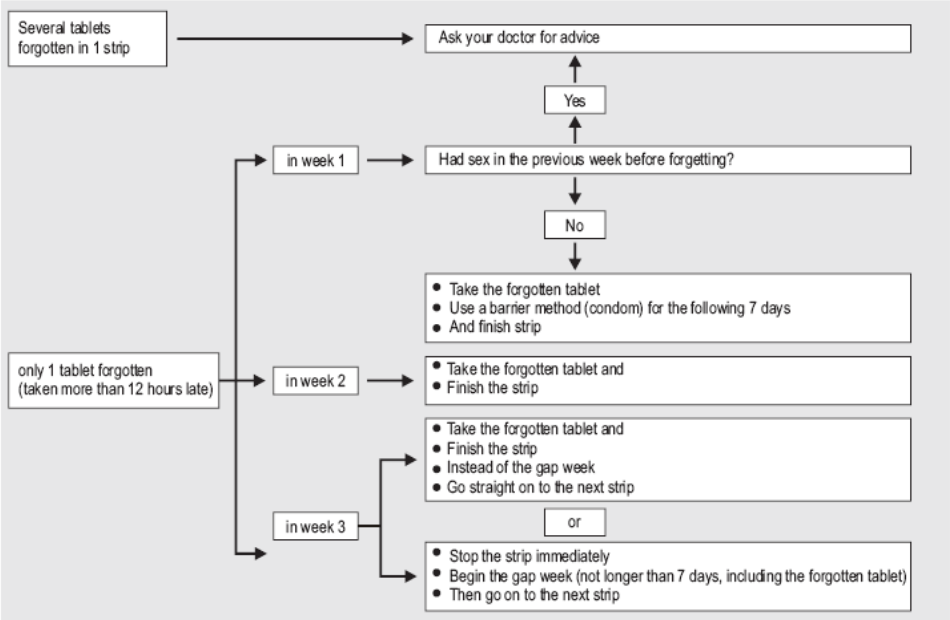
One tablet forgotten in week 2
Take the forgotten tablet as soon as you remember, even if that means that you have to take two tablets at the same time. Take the tablets again at the usual time. The protection from pregnancy is not reduced, given that you have taken the tablets correctly in the previous 7 days, otherwise extra precaution should be used for the next 7 days.

One tablet forgotten in week 3
You can choose between two possibilities:
1. Take the forgotten tablet as soon as you remember, even if that means that you have to take two tablets at the same time. Take the tablets again at the usual time. Instead of the tablet-free period go straight on to the next strip.
Most likely, you will have a period (withdrawal bleed) at the end of the second strip but you may also have spotting or breakthrough bleeding during the second strip.

2. You can also stop the strip and go directly to the tablet-free period of 7 days **(record the day on which you forgot your tablet).** If you want to start a new strip on your fixed start day, make the tablet-free period less than 7 days.

If you follow either of these two recommendations, you will remain protected against pregnancy.

If you have forgotten any of the tablets in a strip, and you do not have bleeding in the first tablet-free period, this may mean that you are pregnant. You must contact your doctor before you go on to the next strip.



What must you do in the case of vomiting or severe diarrhoea
If you vomit within 3-4 hours of taking a tablet or you have severe diarrhoea, there is a risk that the active substance in the pill are not fully adsorbed into your body. The situation is similar to if you forget a tablet. After vomiting or diarrhoea, you must take another tablet from a reserve strip as soon as possible. If possible take it within 12 hours of when you normally take your pill. If this is not possible or 12 hours have passed, you should follow the advice given under 'if you forget to take Femicept.'

Delay of menstrual period: what must you know
Even if not recommended, delay of your menstrual period (withdrawal bleed) is possible by going straight on to a new strip of Femicept instead of the tablet-free period, to the end of the second strip. You may experience spotting (drops or flecks of blood) or breakthrough bleeding while using the second strip. After the usual tablet-free period of 7 days, continue with the following strip.

You might ask your doctor for advice before deciding to delay your menstrual period

Change of the first day of your menstrual period: what you must know

Other serious side effects you should be aware off are also mentioned in section 2 of this leaflet (**Do not take Femicept if you & Take special care with Femicept**). These include:

- Blood clot disorders,
- High blood pressure,
- Liver tumors,
- Swelling of the skin (angioedema),
- Occurrence or deterioration of conditions such as: Crohn's disease, epilepsy, migraine etc.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FEMICEPT

Keep out of the reach and sight of children.
Store below 25° C.
Do not use Femicept after the expiry date which is stated on the carton.

The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

If you take the tablets according to the instructions, then your menstrual period/withdrawal bleed will begin in the tablet-free week. If you have to change this day, do this by making the tablet-free period shorter (but never longer!) For example, if your tablet-free period begins on a Friday, and you want to change this to a Tuesday (3 days earlier) you must start a new strip 3 days earlier than usual. If you make the tablet-free period very short (for example, 3 days or less) then it may be that you do not have any bleeding during this tablet-free period. You may then experience spotting (droplets or flecks of blood) or breakthrough bleeding.
If you are not sure how to proceed, contact your doctor for advice.

If you want to stop taking Femicept

You can stop taking Femicept whenever you want. If you do not want to become pregnant, ask you doctor for advice about other reliable methods of birth control.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Femicept can cause side effects, although not everybody gets them.

Common side effects (affecting more than 1 in 100, but less than 1 in 10 women):
Mood swings, headache, abdominal pain (stomach ache), acne, breast pain, weight gain, nausea

Uncommon side effects (affecting more than 1 in 1000 but less than 1 in 100 women):
Vomiting, diarrhoea, fluid retention, migraine, decreased libido (interest in sex), breast enlargement, itchy red rush of the skin (urticaria).

Rare side effects (affecting less than 1 in 1000 women):
Contact lens intolerance, allergic reactions, weight loss, increased libido (interest in sex, breast discharge, vaginal discharge, allergic reactions which can sometimes be severe with swelling of the skin and/or mucous membranes (erythaema nodosum & eruthema multiforme).

6. FURTHER INFORMATION

Femicept contains

- The active substances are Levonorgestrel (150µg) and Ethinylestradiol (30µg).
- The other ingredients are Lactose Monohydrate, Maize Starch, Povidone K-25, Sucrose, Talc, Calcium carbonate, Povidone K-90, Glycerin, Macrogol 6000, Titanium dioxide, Magnesium Stearate, Carnauba Wax.

What Femicept looks like and contents of the pack
Femicept tablets are white, circular, biconvex and sugar coated.

Each blister pack contains 21 tablets.

Femicept is sold in cartons of 1, 3, 6 or 13 blister packs.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Famy Care Europe Ltd.
One Wood Street,
London, EC2V 7WS,
United Kingdom.

Femicept is manufactured by:
Accord Healthcare Limited
Sage House, 319 Pinner Road,
North Harrow, Middlesex,
HA1 4HF,
United Kingdom

This medicinal product is authorised in the Member States of the EEA under the following names:
UK: Femicept & Levest
DK: Femicept
FI, PL, NL, NO, HU: Oralcon
BE: Levonorgestrel Ethinylestradiol Famy Care

This leaflet was last approved in November 2009

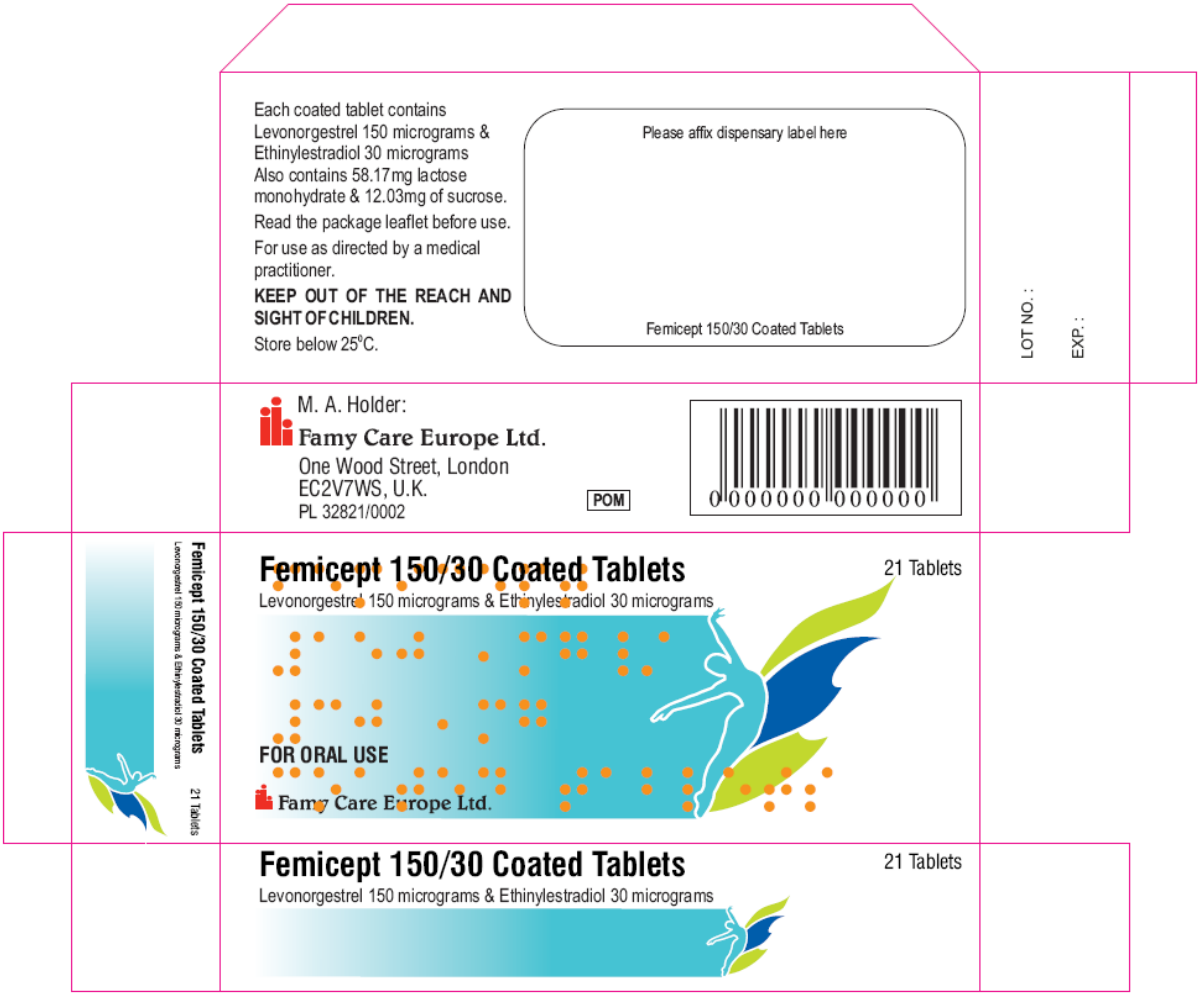
Module 4

Labelling

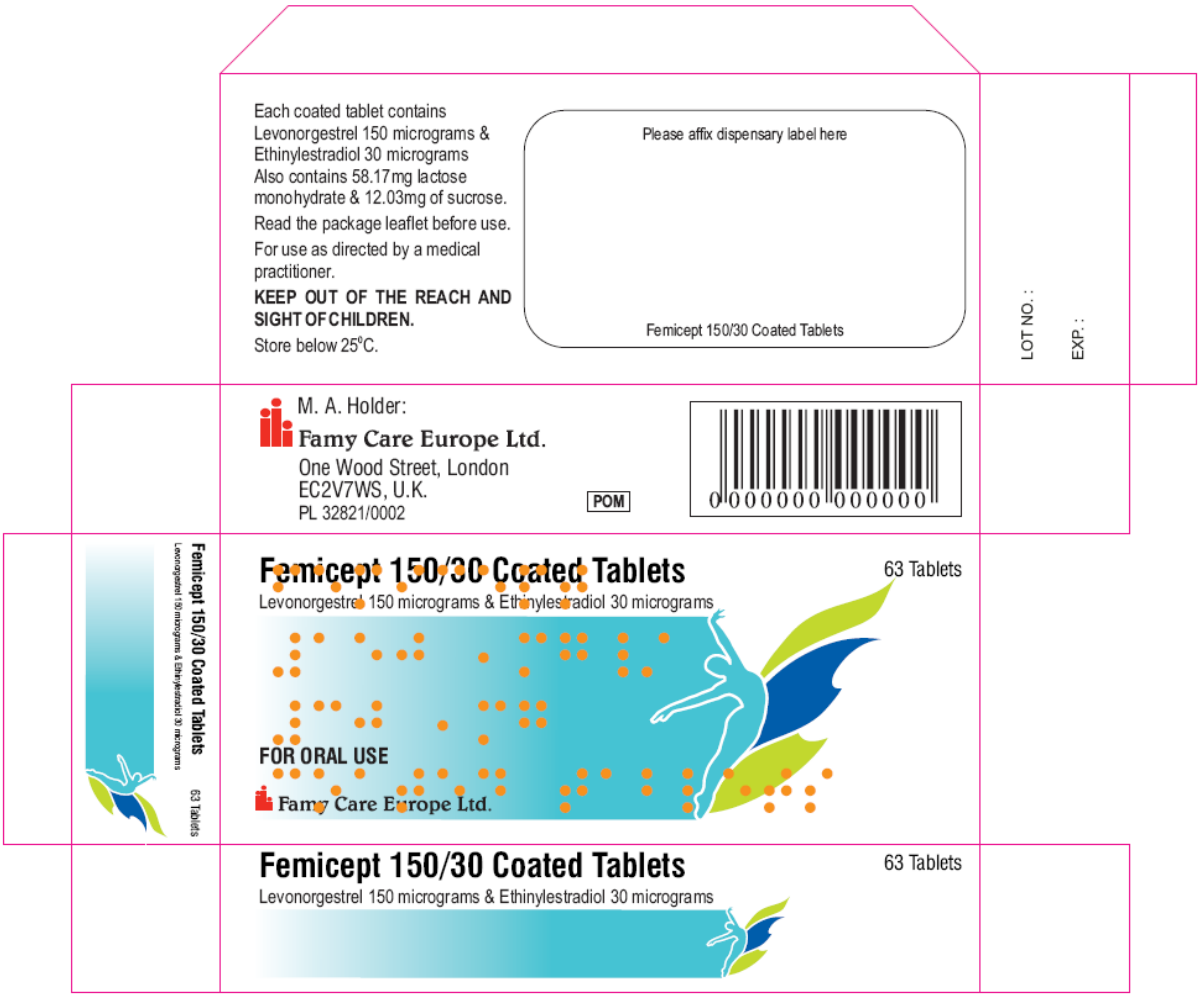
Femicept labelling

Carton with Braille

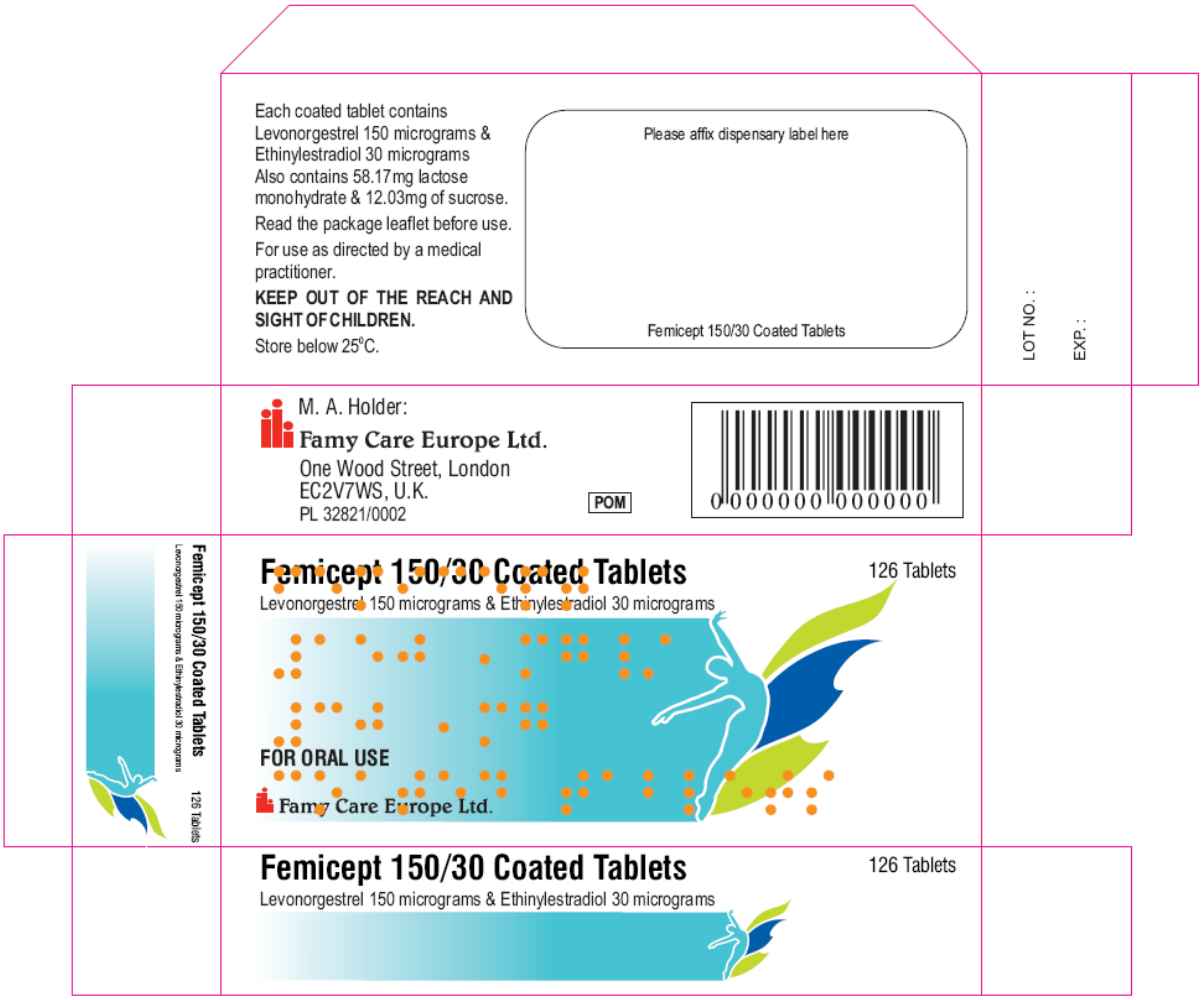
Pack size 21



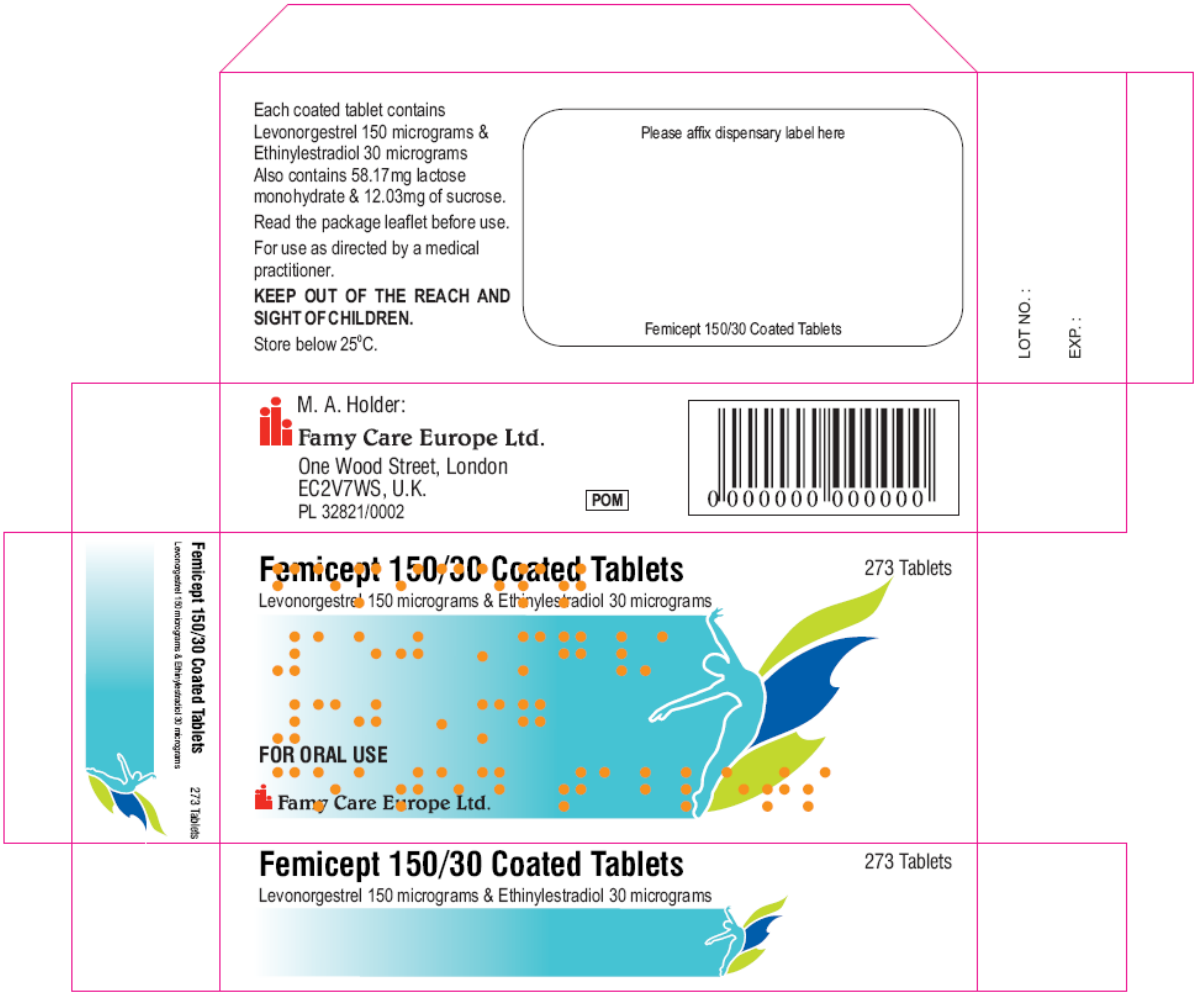
Pack size 63


Each coated tablet contains
Levonorgestrel 150 micrograms &
Ethinylestradiol 30 micrograms
Also contains 58.17mg lactose monohydrate & 12.03mg of sucrose.
Read the package leaflet before use.
For use as directed by a medical practitioner.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Store below 25°C.
Please affix dispensary label here
Femicept 150/30 Coated Tablets
LOT NO. :
EXP. :
M. A. Holder:
Famy Care Europe Ltd.
One Wood Street, London
EC2V7WS, U.K.
PL 32821/0002
POM
0 000000 000000
Femicept 150/30 Coated Tablets
Levonorgestrel 150 micrograms & Ethinylestradiol 30 micrograms
63 Tablets
FOR ORAL USE
Famy Care Europe Ltd.
Femicept 150/30 Coated Tablets
63 Tablets
Levonorgestrel 150 micrograms & Ethinylestradiol 30 micrograms

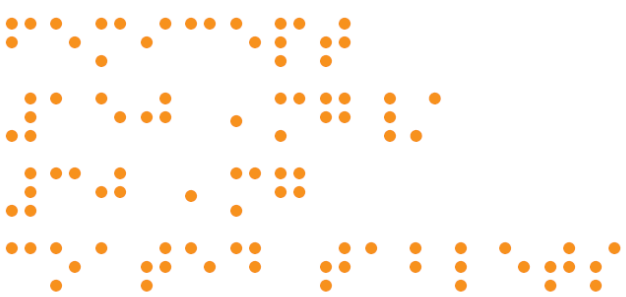
Pack size 126



Pack size 273

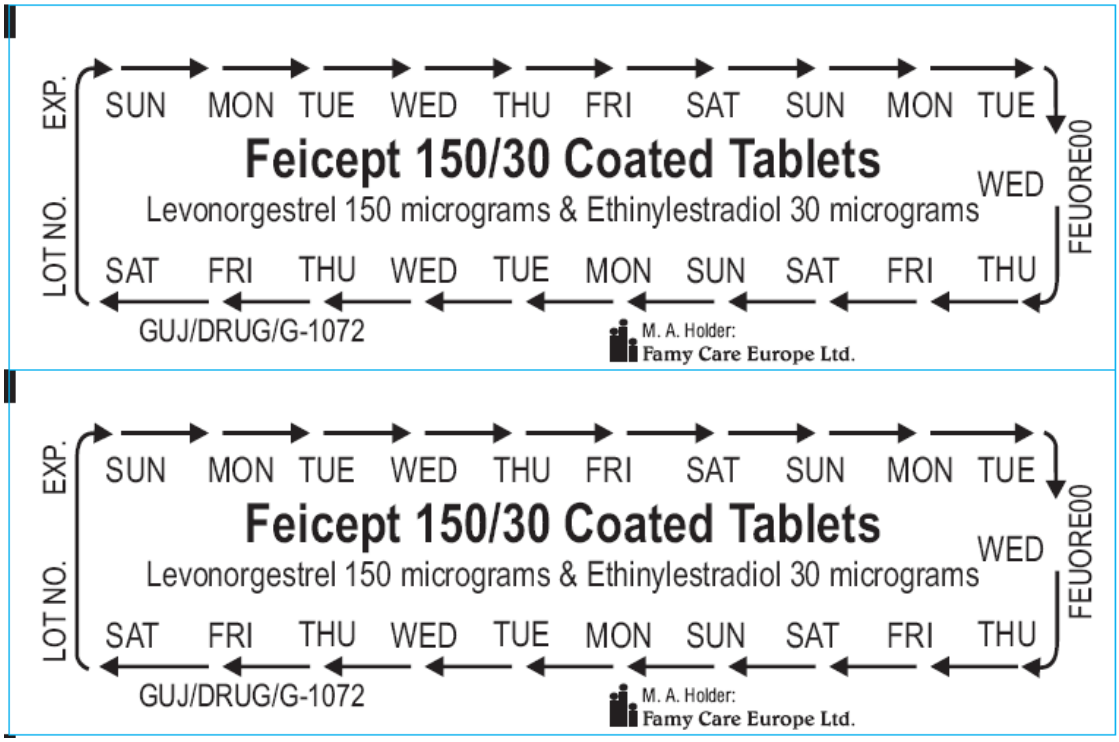


Translation of Braille



Femicept
#150 µg/
#30 µg
Coated Tablets

Blister foil



Levest labelling

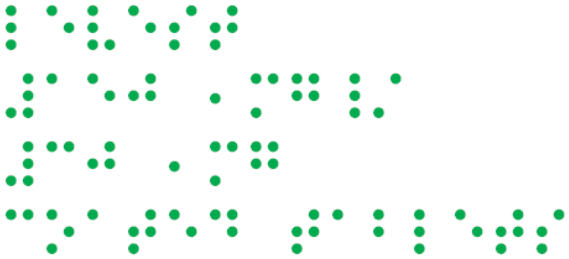
Carton with Braille

Pack size 21

Pack size 63

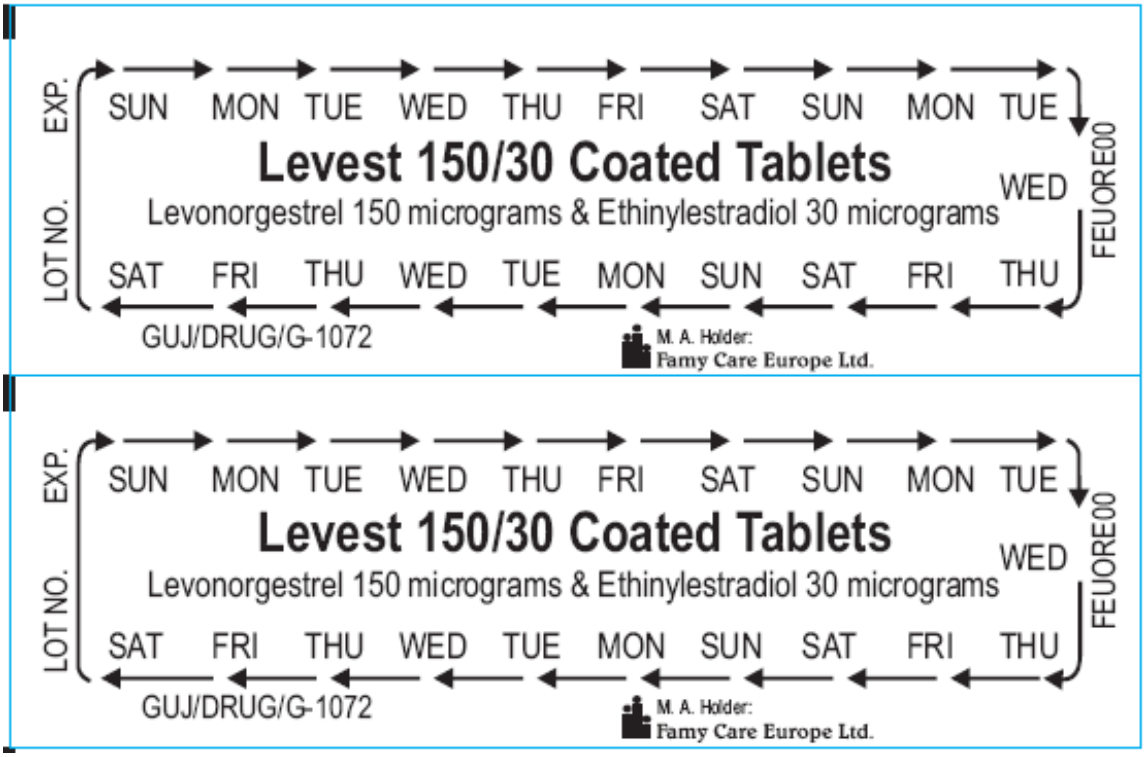

Each coated tablet contains
150 mcg of Levonogestrel
30 mcg of Ethinylestradiol.
Also contains 58.17mg lactose monohydrate & 12.03mg of sucrose.
Read the package leaflet before use.
For use as directed by a medical practitioner.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Store below 25°C.
Please affix dispensary label here
Levest 150/30 Coated Tablets
LOT NO. :
EXP. :
M. A. Holder:
Famy Care Europe Ltd.
One Wood Street, London
EC2V7WS, U.K.
PL 32821/0002
POM
0 000000 000000
63 Tablets
Levest 150/30 Coated Tablets
Levonorgestrel 150 micrograms & Ethinylestradiol 30 micrograms
Levest 150/30 Coated Tablets
Levonorgestrel 150 micrograms &
Ethinylestradiol 30 micrograms
FOR ORAL USE
63 Tablets
Levest 150/30 Coated Tablets
Levonorgestrel 150 micrograms &
Ethinylestradiol 30 micrograms
63 Tablets

Translation of Braille



Levest
#150 µg/
#30 µg
Coated Tablets

Blister foil



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Famy Care Europe Ltd a Marketing Authorisation for the medicinal product Femicept 150 / 30 Coated Tablets / Levest 150 / 30 Coated Tablets (PL 32821/0002, UK/H/1865/001/DC). The product is a prescription-only medicine indicated for oral contraception.

This is an abridged application for Femicept / Levest 150 / 30 Coated Tablets, submitted under Article 10.1 of 2001/83 EC, as amended. The reference product in the UK is Microgynon 30 Tablets, first authorised on 28/11/1973 to Bayer Schering Pharma (PL 00010/0545). The reference product has been authorised in the European Community for more than 10 years, so the period of data exclusivity has expired. With UK as the Reference Member State in this Decentralised Procedure, Famy Care Europe Ltd applied for a Marketing Authorisation for Femicept 150 / 30 Coated Tablets / Levest 150 / 30 Coated Tablets in Belgium, Denmark, Finland, Germany, Hungary, Netherlands, Norway, and Poland.

This product is an oestrogen-progestogen combination which works primarily by inhibiting ovulation. It acts on the hypothalamo-pituitary–ovarian axis to suppress the mid-cycle surge of luteinising hormone (LH). It alters cervical mucus making it impermeable to sperm and renders the endometrium unreceptive for implantation. Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year. The failure rate may increase when pills are missed or taken incorrectly.

No new preclinical or clinical efficacy studies were conducted for this application, which is acceptable given that the application was for a generic version of a product that has been licensed for over 10 years.

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Femicept / Levest 150 / 30 Coated Tablets (Famy Care Europe Ltd), to that of the reference product, Microgynon® 30 (Schering Pharma, Netherlands). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The marketing authorisation holder has provided adequate justification for not submitting a Risk Management Plan (RMP). Femicept / Levest 150 / 30 Coated Tablets is a generic product, the reference product does not have any identified safety concerns which require additional risk management, and the applicant has not provided any.

The applicant has committed to complete a stepwise phase II ERA for both active substances as a follow-up measure in 12-18 months after the grant of the license.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Femicept 150 / 30 Coated Tablets / Levest 150 / 30 Coated Tablets
Name(s) of the active substance(s) (INN)	Ethinylestradiol, levonorgestrel
Pharmacotherapeutic classification (ATC code)	Progestogen and estrogens, fixed combinations (G03A A07))
Pharmaceutical form and strength(s)	Coated tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/1865/001/DC
Reference Member State	United Kingdom
Member States concerned	Belgium, Denmark, Finland, Germany, Hungary, Netherlands, Norway, Poland
Marketing Authorisation Number(s)	PL 32821/0002
Name and address of the authorisation holder	Famy Care Europe Ltd. One Wood Street, London, EC2V 7WS, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

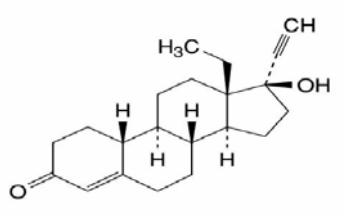
Levonorgestrel

Nomenclature:

INN: Levonorgestrel

Chemical names: 13β-ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one

Structure:



Molecular formula: $C_{21}H_{28}O_2$

Molecular weight: 312.5 g/mol

CAS No: 797-63-7

Physical form: White or almost white, crystalline powder

Solubility: Practically insoluble in water, slightly soluble in alcohol, sparingly soluble in methylene chloride.

The active substance, levonorgestrel, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of levonorgestrel are supported by an EDQM Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of levonorgestrel for inclusion in this medicinal product.

ACTIVE SUBSTANCE

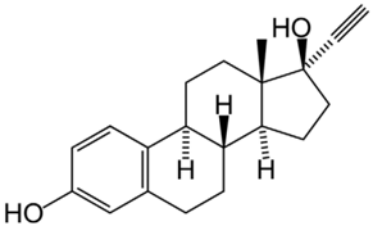
Ethinylestradiol

Nomenclature:

INN: Ethinylestradiol

Chemical names: 19-Nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol

Structure:



Molecular formula: $C_{20}H_{24}O_2$

Molecular weight: 296.4 g/mol

CAS No: 57-63-6

Physical form: White or slightly yellowish-white, crystalline powder

Solubility: Practically insoluble in water, freely soluble in alcohol.

The active substance, ethinylestradiol, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of ethinylestradiol are supported by an EDQM Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of ethinylestradiol for inclusion in this medicinal product.

DRUG PRODUCT

Other ingredients

The finished product is presented as white, circular, biconvex, coated tablets. Each tablet contains 150 micrograms levonorgestrel and 30 micrograms ethinylestradiol

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, maize starch, talc, povidone K25, and magnesium stearate making up the tablet core; and sucrose, talc, calcium carbonate, povidone K-90, glycerol, macrogol 6000, titanium dioxide (E171), and carnauba Wax making up the coating. Appropriate justification for the inclusion of each excipient has been provided.

The excipients are all controlled to the requirements of their current European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

There were no novel excipients used. There is a 20% overage for the coating material to compensate for process losses during coating process.

Dissolution and impurity profiles

Comparative dissolution data were provided for the proposed generic tablet formulation and for an appropriate reference tablet formulation (Microgynon® 30, Schering Pharma, Netherlands). The dissolution profiles were found to be similar and were satisfactory.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided for three batches (c15% of commercial scale) and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished product is licensed for marketing in PVC (polyvinylchloride) - PVdC (polyvinylidene chloride) / aluminium foil blister strips, each containing 21 tablets, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in carton pack sizes of 21, 63, 126 or 273 coated tablets (1, 3, 6, and 13 blisters respectively). The MA Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are ‘Store below 25°C.’.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Femicept / Levest 150 / 30 Coated Tablets, to the reference product, Microgynon® 30 (Schering Pharma, Netherlands).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Quality Overall Summary

A satisfactory QOS is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling and PIL have been provided. The labelling fulfils the statutory requirements for Braille.

Conclusion

The drug product corresponds to the current EU definition of a generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of the active substance and the same pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Femicept / Levest 150 / 30 Coated Tablets is a generic medicinal product of Microgynon 30 Tablets (Bayer plc) is justified.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation has therefore been granted.

III.2 PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for this application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of levonorgestrel and ethinylestradiol, which are widely used and well-known active substances.

A satisfactory non-clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Since both levonorgestrel and ethinylestradiol are likely to act as endocrine disruptors once released in the enviromment, a complete phase II ERA should be conducted irrespective of PECsurfacewater below the action limit or logKow<4.5. According to the EMEA/CHMP/SWP/4447/00 Guideline, the conclusion of the ERA report should be based on sound scientific reasoning supported by adequate studies. The applicant has committed to complete a stepwise phase II ERA for both active substances as a follow-up measure in 12-18 months after the grant of the license.

III.3 CLINICAL ASPECTS

INDICATIONS

Femicept / Levest 150 / 30 Coated Tablets is indicated in oral contraception.

The indication is consistent with that for the reference product and is satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the reference product and satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of levonorgestrel and ethinylestradiol is well known. No novel pharmacodynamic data are supplied or required for this application.

Pharmacokinetics

Absorption
After oral administration, peak serum concentration of levonorgestrel is reached in 1.4 ± 0.3 hours, with concentrations of approximately 5.6 ± 1.5ng/mL. The terminal half life for levonorgestrel after administration of a single dose of levonorgestrel / ethinylestradiol is about 30 hours.

Peak serum concentration of ethinylestradiol of approximately 145pg/mL is reached in about 1.6 hours and terminal half life is approximately 15 hours after administration of a single dose of levonorgestrel / ethinylestradiol.

Distribution
The apparent volume of distribution is reported to be approximately 1.8L/kg for levonorgestrel and 4.3L/kg for ethinylestradiol. Levonogestrel is 97.5-99% protein-bound primarily to sex hormone binding globulin (SHBG) 65% and to a lesser extent serum albumin. Ethinylestradiol is about 95–97% bound to serum albumin but does not bind to SHBG although it induces SHBG synthesis leading to decreased levonorgestrel clearance. Following repeated daily dosing of combination levonorgestrel /ethinylestradiol oral contraceptives, levonorgestrel plasma concentrations accumulate, due in part, to increased SHBG levels that are induced by ethinylestradiol and a possible reduction in hepatic metabolic capacity.

Metabolism
Following absorption, levonorgestrel is conjugated at the 17β-OH position to form sulphate and glucuronide conjugates in plasma. Levonorgestrel and its phase I metabolites are eliminated primarily as glucuronide conjugates.

First-pass metabolism of ethinylestradiol involves formation of ethinylestradiol-3-sulphate in the gut wall, followed by 2-hydroxylation of a portion of the remaining untransformed ethinylestradiol by hepatic cytochrome P-450 3A4 (CYP3A4). Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of ethinylestradiol hydroxylation. Hydroxylation at the 4-, 6-, and 16- positions may also occur, although to a much lesser extent than 2-hydroxylation. The various hydroxylated metabolites are subject to further methylation and/or conjugation.

Excretion
About 45% of levonorgestrel and its metabolites are eliminated in the urine and about 32% are eliminated in faeces, mostly as glucuronide conjugates.

Ethinylestradiol is excreted in the urine and faeces as glucuronide and sulphate conjugates, and it undergoes entero-hepatic recirculation.

Bioequivalence study

The applicant has conducted a single bioequivalence study comparing the pharmacokinetic profiles of Femicept / Levest 150 / 30 Coated Tablets (test) and Microgynon® 30, Schering Pharma, Netherlands (reference). Certificates of Analysis have been provided for both the test and reference product.

This was a conventional; randomised, open-label, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability and bioequivalence study conducted in 30 healthy adult human female subjects under fasting conditions. The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP).

A single dose (2 tablets) of the investigational products was administered orally with 240 ml of water to each subject in each period, after an overnight fast. Treatment periods 1 and 2 were separated by a satisfactory washout period of 31 days. Blood samples were taken pre-dose (0.0) and at specified time points up to 168.0 hours after administration of test or reference product. Plasma samples were analysed for levonorgestrel and ethinylestradiol using an appropriate, validated LC / MS / MS method.

The primary pharmacokinetic parameters for the studies were C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Results:

30 subjects were enrolled in the study. 29 volunteers completed both study periods. One subject was withdrawn from the study due to an adverse event in period 2.

Safety – Eight subjects reported adverse events after the administration of test product. Three subjects reported adverse events after administration of the reference product. The intensity of these events was reported as mild and resolved. One case of diarrhoea was reported after administration of the test product in period 2. All subjects recovered. No deaths or serious AEs were reported during the study.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for levonorgestrel for a randomised, two-way, single dose crossover study between the test and reference products. n=29 healthy subjects, dosed fasted; t=168 hours. Wash-out period: 31 days. Log-transformed values.

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC_{0-inf}	171.84	179.82	95.56	88.51	103.18
AUC_{0-t}	142.98	143.61	99.56	92.22	107.50
C_{max}	9.73	11.36	85.65	80.54	91.09

Pharmacokinetic results for ethinylestradiol for a randomised, two-way, single dose crossover study between the test and reference products. n=29 healthy subjects, dosed fasted; t=168 hours. Wash-out period: 31 days. Log-transformed values.

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC_{0-inf}	1430.61	1539.17	92.95	82.53	104.68
AUC_{0-t}	1026.35	1073.42	95.61	84.96	107.61
C_{max}	144.19	149.50	96.45	91.02	102.21

The 90% confidence intervals of the ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the accepted limits of 80 – 125%, as specified in the CPMP/EWP/QWP/1401/98 Note for Guidance and as pre-specified in the study protocol.

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test and reference products are bioequivalent, after administration of a single dose (2 tablets) under fasted conditions, as the confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80-125% in line with current CHMP guidelines.

Clinical efficacy

No new data have been submitted and none are required. The reference product is established and the application depends upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of levonorgestrel and ethinylestradiol is well-established from their extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profiles of levonorgestrel and ethinylestradiol are well-known.

EXPERT REPORT

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The final SmPC is consistent with that of the innovator product, and is acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

The labelling is satisfactory.

CONCLUSIONS & DISCUSSION

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Femicept / Levest 150 / 30 Coated Tablets) and reference (Microgynon® 30, Schering Pharma) formulations within general acceptance limits.

Sufficient clinical information has been submitted to support this application. A Marketing Authorisation was, therefore, granted on medical grounds.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Femicept / Levest 150 / 30 Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Femicept / Levest 150 / 30 Coated Tablets and the reference product Microgynon® 30 (Schering Pharma).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SmPC, PIL and labelling are satisfactory and consistent with those of the reference product.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The testing shows that patients/users are able to act upon the information that the leaflet contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant's Femicept / Levest 150 / 30 Coated Tablets is a generic medicinal product of the reference product, Microgynon® 30 Tablets (Bayer plc). Extensive clinical experience with levonorgestrel and ethinylestradiol in combination is considered to have demonstrated the therapeutic value of the medicinal product. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

Date submitted	Application type	Scope	Outcome