SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FAMY-POP[1]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains levonorgestrel 30 µg.

Excipient with known effects: Each tablet contains 85.82 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Round, white to off-white, biconvex, film coated tablets, debossed with 'E 'on one side and plain on other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Contraception for women

4.2 Posology and method of administration

Posology

One FAMY-POP daily without tablet-free breaks

Method of administration

The first tablet is removed from a blister pack well marked with the abbreviated day of the week for the start of tablet-taking. The tablets are taken continually in the direction of the arrows, irrespective of whether bleeding occurs.

The day after the tablets from one blister pack have been used up, the first tablet from a new blister pack is taken.

The tablets must be taken at about the same time every day with a sufficient amount of liquid. The interval between two consecutive tablets should be as close as possible to 24 hours. To avoid jeopardizing the contraceptive effect this time must not be exceeded by more than three hours at all events. The maximum reliability of FAMY-POP can only be guaranteed if the time between tablet-taking is kept as close as possible to 24 hours.

Starting to take FAMY-POP

- When not preceded by the taking of hormonal contraceptives (in the previous month)

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Tablet-taking is to start on the first day of the natural cycle (i.e. first day of menstruation). If the taking of FAMY-POP starts later, an additional barrier method of contraception is to be used in the first seven days.

- Switching from a combined oral contraceptive (estrogen/progestogen combination)

The taking of FAMY-POP is started on the day following the taking of the last tablet of the previous preparation that contained active ingredients. The user must be instructed that if the contraceptive used previously also contained tablets without active substances, such latter tablets are not to be taken. This approach ensures uninterrupted contraception.

- Switching from a progestogen-only pill (POP, injectable product, implant)

If another oral progestogen-only pill (POP) was taken previously, the switchover can take place on any day without a tablet-free break. If the tablets were taken correctly, no additional contraceptives measures need be applied.

When switching from an implant, the taking of FAMY-POP must start on the day of removal, and when switching from an injectable product tablet-taking must start at the time the next injection would have been due.
When switching from an implant or injectable product, an additional barrier method of contraception should be used during the first seven days.

- After an abortion in the first trimester

Tablet-taking can start immediately. An additional barrier method should be used during the first seven days.

- After delivery or an abortion in the second trimester

Women who are not breast-feeding can start taking FAMY-POP 21 days after a birth or second-trimester miscarriage. An additional barrier method should be used during the first seven days. If sexual intercourse has already taken place, pregnancy must be ruled out before starting to take FAMY-POP, or the first menstruation should be waited for.

- Use in breastfeeding women (see section 4.6 "Pregnancy and lactation")

<u>What to do when tablets were forgotten</u>
Even if only one tablet was taken late (i.e. if more than 27 hours have elapsed since the last tablet was taken) or if one tablet was forgotten, contraceptive protection may be impaired.

The missed tablet should be taken as soon as possible, even if this means having to take two tablets at the same time. After this, tablet-taking is resumed at the normal time of day. In addition, a barrier method is to be used for the next seven days.

If sexual intercourse has taken place in the previous seven days, the possibility that pregnancy may have occurred should be considered. The risk of pregnancy occurring increases with the number of tablets missed.

<u>What to do in case of vomiting or severe diarrhea</u>
If vomiting or diarrhea occurs within the first three to four hours of tablet-taking, the active substance may possibly not have been completely absorbed by the intestines. In such a case the same advice as

given above for a missed tablet shall apply, i.e. an additional barrier method must be used on the following seven days.
Any replacement tablet(s) should be taken from the end of the current pack so that it is possible to keep an overview of daily tablet-taking from the days of the week shown on the blister pack.

Children and adolescents
FAMY-POP must not be used before the first menstruation occurs.

4.3 Contraindications

FAMY-POP must not be used if any of the following disorders/risk factors apply. If any of these disorders/risk factors occur for the first time while FAMY-POP is being taken, the drug must be stopped immediately.

FAMY-POP must not be used in case of:

- known hypersensitivity to the active substance or any other excipients listed in section 6.1,
- known or suspected pregnancy,
- present venous thromboembolic disorders (deep vein thrombosis, pulmonary embolism),
- past or present arterial and cardiovascular disorders (e.g. cerebrovascular attack, myocardial infarction) or prodromal signs (e.g. angina pectoris and transitory ischemic attack),
- diabetes mellitus with vascular changes
- past or present severe hepatic disorders as long as liver function values have not returned to normal,
- past or present hepatic tumors (benign or malignant),
- known or suspected malignant disorders of the genital organs or breast, provided these are susceptible to sex hormone influence,
- unclarified vaginal hemorrhage.

4.4 Special warnings and precautions for use

Users with the rare congenital fructose intolerance, congenital galactose intolerance, glucose/galactose malabsorption, sucrase-isomaltase deficiency or lactase deficiency should not take FAMY-POP.

Medical examination/consultation

Before FAMY-POP is prescribed for the first time or again at a later date a full medical examination must be conducted (including family history), and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be conducted, bearing in mind the contraindications (see section 4.3) and warnings (see section 4.4). The user must also be advised to read the directions for use carefully and to follow them. The frequency and extent of further regular checkups should be determined on an individual basis and conducted in line with the pertinent recommendations.
It should also be pointed out that the taking of oral contraceptives does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Warnings

If any of the disorders/risk factors listed below is present, the benefit of FAMY-POP should be weighed against the possible risks that might arise for the individual woman and should be discussed with her, before she decides to take it. In case any of these disorders is exacerbated or occurs for the first time, or if risk factors arise, the woman must consult her health care provider. The latter will decide whether the drug must be discontinued or not.

Vascular disorders

Epidemiological studies provide scarcely any evidence for a correlation between the use of hormonal contraceptives that contain a progestogen only and an enhanced risk of sustaining myocardial infarction and cerebral thromboembolism. The risk of sustaining cardiovascular and cerebral events is more closely associated with increasing age, high blood pressure and smoking. The risk of suffering a stroke might be slightly higher in women with high blood pressure taking oral contraceptives with a progestogen only.

Epidemiological studies would imply that the use of combined oral contraceptives may be associated with a higher incidence of venous thromboembolisms (VTE, deep vein thrombosis and pulmonary embolisms). Although the clinical significance of these findings has not been established for levonorgestrel as a contraceptive in the absence of an estrogen component, the taking of FAMY-POP should be discontinued if a thrombosis occurs. One should also consider stopping FAMY-POP in the case of immobilization due to surgery or illness. Women with a history of thromboembolic disorders should be advised of a possible reoccurrence.

The generally recognized risk factors for venous thromboembolism (VTE) include

- a personal or family history of the occurrence of VTE (in a sibling or parent at a relatively young age),
- advancing age,
- obesity (body mass index above 30 kg/m²),
- prolonged immobilization, major surgery, any leg surgery or extensive injuries. In these situations it is advisable to stop taking the POP (in the case of elective surgery at least four weeks in advance) and to restart not earlier than two weeks after complete mobility has been restored. Thrombosis prophylaxis should be considered, if the POP was not discontinued in good time.

The enhanced risk of thromboembolism in the puerperium must also be taken into account.

Taking must be discontinued immediately any symptoms of an arterial or venous thrombosis occur or if this is suspected.

Symptoms of venous or arterial thrombosis may be:

- unusual pain or swellings in a leg,
- sudden severe pain in the chest, possibly radiating to the left arm,
- sudden difficulty in breathing,
- sudden coughing bout,
- unusual, severe or persistent headache,
- sudden partial or complete loss of vision,
- diplopia,
- slurred speech or aphasia,
- vertigo,
- collapse with or without focal seizure,
- sudden weakness or pronounced numbness in one half or part of the body,
- disorders of the motor functions,
- "acute" abdomen.

Tumors

Breast

A meta-analysis involving 54 epidemiological studies pointed to a slightly enhanced relative risk (RR= 1.24) for breast cancer occurring in women currently taking combined oral contraceptives. The enhanced risk gradually declines over the 10 years after the combined oral contraceptives are no longer used.

Since breast cancer is rare in women below the age of 40, the number of additional cases of breast cancer diagnosed in current or previous users of combined oral contraceptives is low in comparison to the overall risk.

The risk of breast cancer being diagnosed in the users of progestogen-only preparations is probably of the same order of magnitude as that determined in connection with combined oral contraceptives. It must be borne in mind, however, that any indications in respect of progestogen-only preparations are based on a much smaller population of users and are therefore less conclusive than those concerning combined oral contraceptives. These studies do not provide any evidence of a causal link.

The findings may be due to a timelier diagnosis, the actual effects of the hormonal contraceptives, or a combination of both.

In women who took oral contraceptives it appears that the developmental stage of any breast cancer diagnosed was clinically less advanced than cancer diagnosed in nonusers.

Liver
In rare cases benign liver tumors, and even more rarely malignant liver tumors, were found in women taking oral contraceptives. In isolated cased these tumors led to life-threatening hemorrhages in the abdominal cavity. Differential diagnosis should include hepatic tumors if severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women on oral contraceptives.

Other conditions
In general progestogen-only preparations appear to have no effect on blood pressure in normotensive women. If, however, a persistent, clinically significant, rise in blood pressure should develop during the use of FAMY-POP, the latter should be discontinued.

Likewise, a recurrence of cholestatic icterus or cholestasis-conditioned pruritus that occurred in a previous pregnancy or during earlier use of steroidal sex hormones make it necessary to stop using FAMY-POP.

Since FAMY-POP may have an influence of peripheral insulin resistance and glucose tolerance, diabetics and any women who had diabetes mellitus during a past pregnancy must be closely monitored, especially in the initial period of use of this drug.

On occasions, chloasma may occur, particularly in women with a history of *chloasma gravidarum*. Women who are susceptible to this should therefore not expose themselves to direct sunlight or ultraviolet light when taking FAMY-POP.

Ectopic pregnancy
Ectopic pregnancies occur more frequently in users of FAMY-POP than in users of combined oral contraceptives. For this reason FAMY-POP should only be used by women with a history of extrauterine pregnancy or tubal deficiency (e.g. in the case of present or past salpingitis or if only one tube is present) after carefully analyzing the risks and benefits.

If pain in the lower abdomen occurs with an irregular cycle (amenorrhea or amenorrhea followed by continuous bleeding), the possibility of an ectopic pregnancy must be considered.

Persisting ovarian follicle
During the use of FAMY-POP persisting ovarian follicles (often also called functional ovarian cysts) may occur. The majority of these follicles remain without symptoms, but some may be accompanied by pain in the lower abdomen or dyspareunia. In most cases these enlarged follicles disappear of their own accord during two to three months of observation.

Reduced efficacy
The efficacy of FAMY-POP can be impaired if, one or several tablets are missed or taken late (see section 4.2), vomiting or severe diarrhea occurs (see section 4.2), certain other drugs are taken at the same time (see section 4.5), FAMY-POP and preparations containing St-John's wort are taken at the same time (see section 4.5).

Cycle disturbances
Cyclical bleeding
In the majority of all cases bleeding is cyclical and at normal intervals, of normal duration and intensity. Nevertheless, shorter or longer intervals have also been observed.

For this reason the user should be informed before she starts taking the tablets that such changes in bleeding patterns are possible. The changes mainly occur in the initial months of use. Later on during use the bleeding pattern settles down and in most cases an individual pattern is established. The user should be instructed to note all bleeding occurrences in a calendar.

What to do in the case of intermenstrual bleeding
Intermenstrual bleeding of varying intensity may occur, particularly during the initial months. From the medical point of view this is no reason to stop taking FAMY-POP, provided organic reasons for such bleeding can be ruled out by suitable diagnostic means.

No attempt should be made to treat cyclical disturbances by administering additional estrogen. Such an approach would lead to a reversal of the changes in the cervical mucus brought about by FAMY-POP, thus considerably jeopardizing contraceptive reliability.

If cyclical bleeding fails to occur
In some women amenorrhea may occur, but in most cases this lasts only one or two cycles. In rare cases the amenorrhea may persist for longer periods of time.

If bleeding fails to occur again within six weeks from the last bleeding, pregnancy must be ruled out before further tablets are taken.

4.5 Interactions with other medicinal products and other interactions

Influence of other medications on FAMY-POP

Drug interactions causing an enhanced clearance of sexual hormones may lead to breakthrough bleeding and a failure of oral contraceptives. This effect has been demonstrated for many active substances that induce hepatic enzymes (e.g. hydantoins like phenytoin, barbiturates like phenobarbital, primidone, carbamazepine, rifampicin, oxcarbazepine, herbal medicines containing St. John's wort (*Hypericum perforatum*) and rifabutin. This is also suspected in the case of efavirenz, nevirapine, topiramate, felbamate, ritonavir, nelfinavir and griseofulvin.

Women using a drug of the above substance category for a short period (up to one week) should use a barrier method in addition to FAMY-POP, i.e. during the period of treatment with the concomitant medication and for a further 28 days after that drug has been stopped.

If a prolonged treatment with drugs that induce hepatic enzymes is needed, or if continued irregular bleeding occurs owing to interactions between the drugs, a different contraceptive method should be suggested.

Oral contraceptives are also reported to have failed when antibiotics such as ampicillins and tetracyclines were taken. The mechanism of this interaction has not been clarified so far.

Treatment with activated charcoal can diminish the absorption of the active substance levonorgestrel, thus reducing contraceptive reliability. In this case the notes in section 4.2 should be followed.

Influence of FAMY-POP on other medications

Oral contraceptives may impair the metabolism of other medicinal products. Consequently the plasma and tissue levels (e.g. of cyclosporin) can be impaired.

Note: You should refer to the Summary of Product Characteristics of the respective concomitant medication for any possible interactions.

Laboratory tests
The use of hormonal contraceptives may impair certain laboratory test findings, including biochemical parameters for hepatic, thyroid, adrenal and renal functions as well as plasma levels of (vector) proteins, e.g. of corticosteroid-binding globulin and of lipid/lipoprotein fractions, parameters for carbohydrate metabolism and coagulation and fibrinolysis parameters. As a rule, however, these changes remain within the normal range.

4.6 Fertility, pregnancy and lactation

Pregnancy
FAMY-POP must not be used during pregnancy.

Pregnancy must be ruled out prior to the start of drug administration. If pregnancy occurs under treatment, the drug product must be discontinued immediately.

Data from a limited number of pregnancies exposed to this drug show no deleterious effects on the fetus for levonorgestrel on its own.
Animal experimental studies have demonstrated reproduction toxicity (see section 5.3).
Undesired hormonal effects on the development of the urogenital tract cannot be completely ruled out, but most of the epidemiological studies carried out to date do not indicate any enhanced risk of deformities occurring in the offspring of mothers who took contraceptives prior to pregnancy, nor are there any indications of an embryotoxic or teratogenic effect coming about through accidental ingestion of progestogens during pregnancy at doses like those contained in FAMY-POP.

Breastfeeding
During breastfeeding hormonal contraceptives are not recommended as the method of choice for contraception. After the nonhormonal methods, progestogen-only preparations are regarded as the next best choice for contraception.

If progestogen-only preparations are used six weeks after the birth, there appear to be no detrimental effects on the growth and development of the breastfed infant. There is no evidence to suggest that progestogen-only preparations impair either quality or quantity of breast milk, although small amounts of the active substance are excreted with the milk.

4.7 Effects on ability to drive and use machines

FAMY-POP has no or only a negligible effect on the ability to drive or operate machines.

4.8 Undesirable effects

In the assessment of side effects the following frequency brackets are used:

Very common	(≥ 10%)
Common	(≥ 1% to < 10%)
Uncommon	(≥ 0.1% to < 1%)
Rare	(≥ 0.01% to < 0.1%)
Very rare	(< 0.01% or unknown)

The following side effects have been reported following the use of FAMY-POP.

	Incidence of side effect			
Body system category	**Very common ≥ 10%**	**common ≥ 1% - < 10%**	**uncommon ≥ 0.1% - < 1%**	**Rare ≥ 0.01% - < 0.1%**
Immune system diseases				hypersensitivity reactions
Psychiatric conditions		depressed moods, changes in libido		
Nervous system conditions		headache, dizziness, nervousness		
Eye conditions				poor tolerance of contact lenses
Gastrointestinal tract conditions		nausea, vomiting		
Skin and subcutaneous tissue disorders		acne	chloasma	hirsutism, skin disorders
Genital organs and breast conditions	bleeding disturbances such as spotting, intermenstrual bleeding or amenorrhea	breast pain, breast tension, dysmenorrhea, vaginitis, menorrhagia*, metrorrhagia*		changes in vaginal secretion
General diseases			fluid retention in the tissues	
Tests:				changes in body weight

* applies generally to all progestogen-only preparations

See section 4.4 for further serious side effects, such as thromboembolic diseases, hepatic tumors, cervical and breast cancer.

Ectopic pregnancies occur more frequently in users of hormonal contraceptives that contain a progestogen only (so-called POPs) than in users of combined oral contraceptives (see section 4.4). During the use of FAMY-POP persisting ovarian follicles (often also called functional ovarian cysts) may occur (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

There have been no reports of any serious damage to health caused by an overdose.

The symptoms that may occur in such a case include: nausea, vomiting and mild vaginal bleeding. There is no special antidote. Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens, ATC code: G03AC03

FAMY-POP contains the orally effective progestogen levonorgestrel at a very low dose.

The continuous daily ingestion of 30 µg levonorgestrel prevents conception by various separate mechanisms.

FAMY-POP mainly acts via its peripheral progestogenic effect on cervical mucus, the tubes and the endometrium. This prevents ascension of the sperms as well as disturbing the transport and implantation of the ovum. Ovulation is inhibited in few women. FAMY-POP impairs the gonadotropin peak in the middle of the cycle and the *corpus luteum* function, which can also contribute to the contraceptive effect.

POPs are particularly suitable for women in whom estrogens are contraindicated or not desired, and also for breastfeeding women, starting six weeks after childbirth.

The contraceptive reliability of POPs is somewhat lower than with combined oral contraceptives. If taken properly, the risk of becoming pregnant is however very low, comparatively speaking.

In clinical studies in which 3,218 women took FAMY-POP for up to two years, involving 28,000 menstrual cycles, 90 pregnancies occurred. Taking all these pregnancies into account, including those occasioned by incorrect tablet-taking, the Pearl Index for FAMY-POP amounts to 4.14.

5.2 Pharmacokinetic properties

Absorption
Levonorgestrel is rapidly and almost completely absorbed on oral administration.

Following single dose administration of FAMY-POP in healthy volunteers, the mean (± SD) levonorgestrel Cmax value was 4.11 (± 1.97) ng/ml and the corresponding value for AUC was 42.3 (± 25.1) ng·hour/ml. The median (range) tmax value was 1.0 (0.75-1.5) hours.

Distribution
Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only approx. 1.5 % of the total levonorgestrel serum concentration is in the form of free levonorgestrel; approx. 65 % is specifically bound to SHBG. The relative distribution of serum levonorgestrel (free, albumin-bound and SHBG-bound) depends on the actual level of SHBG. Upon ingestion of FAMY-POP the serum level of SHBG may fall slightly, and this will have a slight effect on the relative distribution of levonorgestrel with respect to the two binding proteins. The apparent volume of distribution of levonorgestrel is approx. 106 L.

Levonorgestrel passes into the mother's milk. About 0.1 % of the maternal dose can be transferred to the infant during breastfeeding.

Metabolism
Levonorgestrel is fully metabolized via the known metabolic pathways of steroid metabolism. No pharmacologically active metabolites are known.

The metabolic clearance rate from serum is between 1 and 1.5 mL/min/kg.

Elimination
Levonorgestrel serum levels fall in two phases, characterized by half-lives of about one hour and 20 hours respectively.

Elimination of the metabolites is roughly equally shared between the urine and feces. Metabolite elimination half-life is about one day.

Steady-state conditions

After repeated daily ingestion of levonorgestrel serum levels roughly double and reach steady-state conditions after about five days. The pharmacokinetic properties of levonorgestrel are influenced by the serum levels of SHBG. A daily intake of 150 µg levonorgestrel (equivalent to five times the daily dose of FAMY-POP) led to a 50% drop in SHBG serum levels and thus to a 40% fall in the trough levels of levonorgestrel after two to three weeks.

5.3 Preclinical safety data

The toxicity profile of levonorgestrel is well known. In animal experiments levonorgestrel demonstrated an embryolethal effect and at high doses a virilization effect on female fetuses. Reproduction toxicological studies in rats, mice and rabbits showed no signs of a teratogenic effect. On the strength of conventional studies into safety pharmacology, toxicity after repeated dosage, reproduction toxicology, genotoxicity and carcinogenic potential, the preclinical findings reveal no special risk to humans aside from the information already listed in other sections. On the other hand it must be remembered that sex hormones can promote the growth of hormone-dependent tissue and tumors.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core
Colloidal silicon dioxide, lactose monohydrate, magnesium stearate and povidone.

Tablet coating
Hypromellose, polyethylene glycol, talc and titanium dioxide.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

36 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from light. Store tablets in blisters in the provided carton.

6.5 Nature and contents of container

PVC/PVdC-Al blister containing 28 tablets. Each carton contains 3 blisters of 28 tablets.

PVC/PVdC-Al blister containing 35 tablets. Each carton contains 3 blisters of 35 tablets.

6.6 Special precautions for disposal

No special requirements

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

7. SUPPLIER

Mylan Laboratories Limited
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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

RH057

9. DATE OF FIRST PREQUALIFICATION

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February 2017. Section 6 updated in June 2017.

Reference list

References:

SmPC for Microlut® 30 microgrammes, coated tablets: https://extranet.who.int/prequal