SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Elevin 30 micrograms/150 micrograms film-coated tablets

Leandra 30 micrograms/150 micrograms film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 30 micrograms of ethinylestradiol and 150 micrograms of levonorgestrel

Excipient with known effect
Each film-coated tablet contains 54.84 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Brownish, round convex, film-coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

The decision to prescribe Elevin Tablets should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Elevin Tablets compares with other combined hormonal contraceptives (CHCs), see sections 4.3 and 4.4.

4.2 Posology and method of administration

Method of administration: oral use

Posology

How to take Ethinylestradiol/Levonorgestrel

The tablets must be taken every day at about the same time, if necessary with a little liquid, in order shown on the blister pack. 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. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

How to start the use of Ethinylestradiol/Levonorgestrel

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

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). It is also possible to start between the second and fifth day of the menstrual period, but in that case the woman should be advised to use an additional non-hormonal contraceptive method during the first 7 days.

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

The woman should start with Ethinylestradiol/Levonorgestrel preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Ethinylestradiol/Levonorgestrel preferably on the day of removal, but at the latest when the next application would have been due.

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

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

• Following first-trimester abortion

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

• Following delivery or second-trimester abortion

As the risk of thromboembolic events is elevated in the period immediately following childbirth, the administration of oral contraceptives should not be started earlier than 28 days after childbirth in women who are not breast-feeding or after an abortion in the second trimester. A non-hormonal contraceptive method should also be used during the first 7 days.
However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

For breastfeeding women see section 4.6.

Duration of administration
Ethinylestradiol/Levonorgestrel can be used for as long as a hormonal method of contraception is desired, and the benefits of hormonal contraception outweigh the health risks (for more information on regular check-ups, see section 4.4).

Management of missed tablets

Ethinylestradiol/Levonorgestrel contains a low dose of both hormones. As a result, the contraceptive efficacy margin is small if a pill is missed.

If the user is **less than 12 hours** late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced.
If the usual withdrawal bleeding following the forgotten administration fails to appear, pregnancy must be ruled out before a new blister pack is started.

The management of missed tablets can be guided by the following two basic rules:

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

2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

● Week 1

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a

pregnancy should be considered. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

● Week 2

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if she has missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

● Week 3

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

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next blister pack must be started as soon as the current blister pack is finished, i.e., no gap should be left between packs. The user is unlikely to have a withdrawal bleed until the end of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. The woman may also be advised to discontinue tablet-taking from the current blister pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next blister pack.

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

Advice in case of gastro-intestinal disturbances

In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3- 4 hours after tablet-taking, a new (replacement) tablet should be taken as soon as possible. The new tablet should be taken within 12 hours of the usual time of tablet-taking if possible. If more than 12 hours elapse, the advice concerning missed tablets, as given in section 4.2 “Management of missed tablets”, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister pack.

How to postpone a withdrawal bleed

To delay a period the woman should continue with another blister pack of Ethinylestradiol/Levonorgestrel without a tablet-free interval. The extension can be carried on for as long as wished maximally until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting more frequently. Regular intake of Ethinylestradiol/Levonorgestrel is then resumed after the usual 7-day tablet-free interval.
To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming tablet-free interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the presence of any of the following conditions. Should any of the conditions appear for the first time during CHC use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
    - Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE]).
    - Known hereditary or acquired predisposition for venous thromboembolism, such as APC resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
    - Major surgery with prolonged immobilisation (see section 4.4)
    - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)

- Presence or risk of arterial thromboembolism (ATE)
    - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
    - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
    - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant), thrombogenic valvulopathy or thrombogenic arrhythmia.
    - History of migraine with focal neurological symptoms
    - A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
        - Diabetes mellitus with vascular symptoms
        - Severe hypertension
        - Severe dyslipoproteinaemia

- Smoking (see section 4.4)

- existing or previous pancreatitis if this is associated with severe hypertriglyceridaemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- Undiagnosed amenorrhoea
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Elevin is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

4.4 Special warnings and precautions for use

Reasons for the immediate cessation of Ethinylestradiol/Levonorgestrel intake (see section 4.3):

- pregnancy or suspected pregnancy
- initial symptoms of inflammation of the veins or symptoms of a possible thrombosis (including retinal thrombosis), embolism or myocardial infarction (see “Warnings” further below)
- consistently elevated blood pressure with values above 140/90 mmHg. Renewed administration of COCs can be considered as soon as the blood pressure values have normalised under antihypertensive treatment.
- planned operations (at least 4 weeks beforehand) and/or longer periods of immobilisation (e.g. after accidents). Administration should be restarted no earlier than 2 weeks after complete remobilisation.
- first occurrence or worsening of a migraine
- if headaches occur unusually often, continuously or strongly, or sudden focal neurological symptoms develop (possible first signs of a stroke)
- severe upper abdominal pain, liver enlargement or symptoms of intra-abdominal bleeding (possible indications of a liver tumour)

- occurrence of jaundice, hepatitis, generalised pruritus, cholestasis and abnormal liver values. Steroid hormones are metabolised to a decreased extent in patients with impaired liver function.
- acute derailment of diabetes mellitus
- appearance or reappearance of porphyria

Diseases/risk factors that require special medical monitoring:

- smoking
- women over the age of 35 (see "Warnings" further below)

Warnings

- If any of the conditions/risk factors mentioned below is present, the suitability of Elevin should be discussed with the woman
- In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of Elevin should be discontinued.

Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. The VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

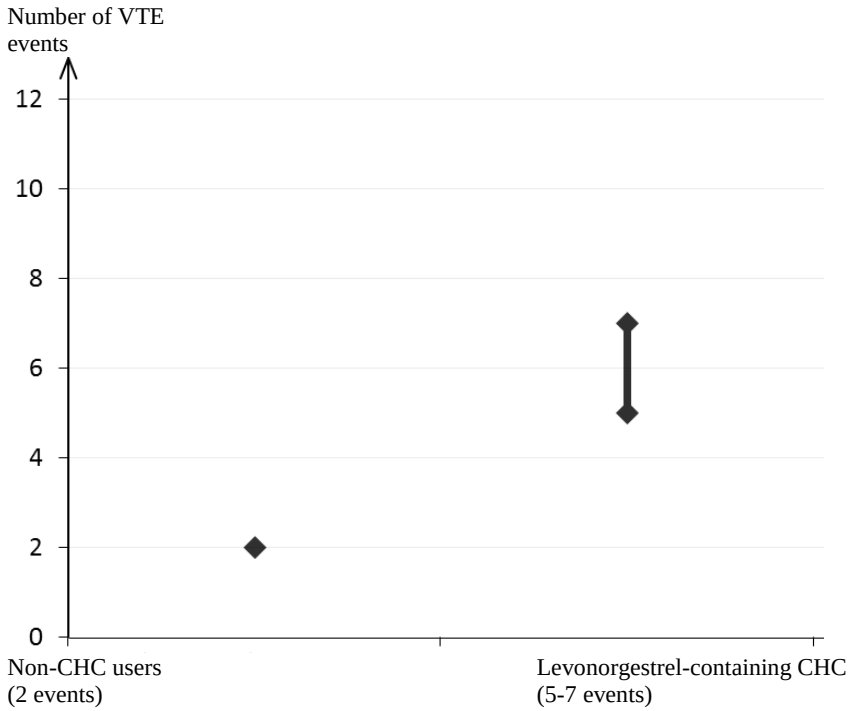
In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

About 6[1] out of 10,000 women who use a levonorgestrel-containing CHC and are not pregnant suffer VTE over the course of a year.

The number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period. VTE may be fatal in 1-2% of the cases.

Number of VTE events per 10,000 women in one year

[1] Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6



Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

Risk factors for VTE

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).

Elevin is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index over 30 kg/m²)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.

Risk factor	Comment
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors	In these situations it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Elevin has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease
Increasing age	Particularly above 35 years
In the first 4 weeks after a birth or a miscarriage in the second trimester	See also section 4.2

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism in pregnancy, and particularly the 6-week period of the puerperium, must be considered (for information on "Pregnancy and lactation" see section 4.6).

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or walking

- Increased warmth in the affected leg; red or discoloured skin on the leg

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may be associated with haemoptysis
- sharp chest pain
- severe light headedness or dizziness
- rapid or irregular heartbeat

Some of these symptoms (e.g. “shortness or breath”, “coughing”) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections)

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.
If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE

The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). Ethinylestradiol/Levonorgestrel is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	**Comment**
Increasing age	Particularly above 35 years
Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 30 who continue to smoke should be strongly advised

Risk factor	Comment
	to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of a cerebrovascular accident can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding;
- sudden trouble seeing in one or both eyes;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:

- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;
- discomfort radiating to the back, jaw, throat, arm, stomach;
- feeling of being full, having indigestion or choking;

- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

Tumours

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

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent 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 ever- users 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 intra- abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

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

Other conditions

Women with hypertriglyceridemia, 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. If, during the use of a COC in preexisting hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstones; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham’s chorea; herpes gestationis; otosclerosis-related hearing loss.

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

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

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

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

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 Elevin 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) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of Elevin compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

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 hormonal contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

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

If COCs and St John's wort are taken concomitantly, an additional non-hormonal contraceptive method is recommended (see section 4.5).

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.

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.

If both have been ruled out, Ethinylestradiol/Levonorgestrel can be taken again or the woman can switch to another preparation. If the COC is not taken regularly or is taken in combination with certain other medicinal products, bleeding during the cycle may occur, which could be an indication of a reduced contraceptive efficacy (see sections 4.2 and 4.5).

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.
It can take a longer time for a normal cycle to return after hormonal contraceptives are discontinued. In some women, amenorrhea (possibly with anovulation) or oligomenorrhoea may occur, particularly if these cycle disorders occurred previously.

Precautions for use

This medicinal product contains lactose.
Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

- Effects of other medicinal products on Elevin

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure/

Management

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Short-term treatment

Women on treatment with enzyme-inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its 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.

Long-term treatment

In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

The following interactions have been reported in the literature.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme induction), e.g.:

Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (Hypericum perforatum). Herbal supplements containing St John’s wort (Hypericum perforatum) should not be used concomitantly with Ethinylestradiol/Levonorgestrel tablets as these may reduce the contraceptive effectiveness of Ethinylestradiol/Levonorgestrel. Break-through bleeding and unintended pregnancies have been reported. The enzyme-inducing effect may last up to 2 weeks after treatment with St. John’s wort is discontinued.

Substances with variable effects on the clearance of COCs:

When co-administered with COCs, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

The following active substances can increase the serum concentration of the sexual steroids contained in Ethinylestradiol/Levonorgestrel (enzyme inhibitors)

- active substances that impede ethinylestradiol in the stomach/intestinal wall, such as ascorbic acid or paracetamol
- atorvastatin (increase in the AUC of ethinylestradiol by 20%)
- active substances that inhibit the microsomal enzymes in the liver (strong and moderate CYP 3A4 inhibitors) such as imidazole antimycotic agents (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin, troleandomycin), diltiazem and grapefruit juice may increase plasma levels of oestrogen or progestogen or both

Substances decreasing the clearance of COCs (enzyme inhibitors):

The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the estrogen or the progestin or both.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0.035 mg ethinylestradiol.

- Effects of Elevin on other medicinal products

Troleandomycin can increase the risk of intrahepatic cholestasis if administered concomitantly with COCs.

COCs may affect the metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

Ethinylestradiol/ Levonorgestrel can affect the metabolism of other active substances:
- by means of the inhibition of hepatic microsomal enzymes resulting in elevated serum concentrations of active substances such as diazepam (and a number of other benzodiazepines), cyclosporin, theophylline, melatonin, tizanidine and glucocorticoids
- through the induction of hepatic glucuronidation resulting in decreased serum levels, for example, of clofibrate, morphine, lorazepam (as well as some other benzodiazepines) and lamotrigine

In vitro ethinylestradiol is a reversible inhibitor of CYP 2C19, CYP 1A1 and 1A2 as well as a mechanism based inhibitor of CYP3A4 / 5, CYP 2C8 and CYP 2J2. In clinical trials, the use of a hormonal contraceptive containing ethinylestradiol did not lead to an increase, or to only a slight increase, in the plasma levels of CYP3A4 substrates (e.g.midazolam) while plasma levels of CYP1A2 substrates were able to be increased slightly (e.g. theophylline) or moderately (e.g. tizanidine). The requirement for insulin or other oral antidiabetics can be different as a result of a change in glucose tolerance.

- Pharmacodynamic interactions

During clinical trials with patients treated for hepatitis C virus infections (HCV) with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see section 4.3).

Therefore, Elevin-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these drug regimens. Elevin can be restarted 2 weeks following completion of treatment with these drug regimens.

- 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 coagulation and fibrinolysis. Changes generally remain within the normal laboratory range. The type and extent of the effects are partially dependent on the dose of the hormones used.

4.6 Fertility, pregnancy and lactation

Pregnancy

Elevin is not indicated during pregnancy.

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

Animal studies have shown undesirable effects during pregnancy and lactation (see section 5.3). Based on these animal data, undesirable effects due to hormonal action of the active compounds cannot be excluded. However, general experience with COCs during pregnancy did not provide evidence for an actual undesirable effect in humans.

The available data regarding the use of Elevin during pregnancy are too limited to permit conclusions concerning negative effects of Elevin on pregnancy, health of the foetus or neonate. To date, no relevant epidemiological data are available.

The increased risk of VTE during the postpartum period should be considered when re-starting Elevin (see section 4.2 and 4.4).

Breastfeeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Description of selected adverse reactions

The administration of combined oral contraceptives is associated with an increased risk of:

- arterial and venous thromboembolic diseases (e.g. venous thromboses, pulmonary embolisms, cerebrovascular events [ischaemic and haemorrhagic stroke, transitory ischaemic attacks], heart attack)
- benign liver tumours (e.g. focal nodular hyperplasia, hepatic adenoma)
- intraepithelial cervical neoplasias and cervical carcinoma
- breast cancer

The most frequent (≥1/10) adverse reactions associated with use of Elevin are headache (including migraine), spotting and intermenstrual bleeding.

Furthermore, the following adverse reactions were reported with the use of ethinylestradiol/levonorgestrel-containing combined oral contraceptives. The following categories have been defined for indicating the frequency of adverse reactions:

Frequency of adverse reactions:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000
Not known: cannot be estimated from the available data

ystem Organ Class	**frequency of undesirable effects**					
	very common	**common**	**uncommon**	**Rare**	**very rare**	**not known**
ıfections and ıfestations		vaginitis, including candidiasis				
leoplasms enign, ıalignant and nspecified ncl cysts and olyps)					Hepatocellular carcinoma	
nmune ystem isorders				Allergic reactions angiooedema, severe anaphylactic/anaphylactoid reactions with respiratory and circulatory symptoms; hypersensitivity		Exacerbation of symptoms of hereditary and acquired angioedema.
letabolism nd nutrition isorders			changes in appetite (increase or decrease) glucose intolerance			
sychiatric isorders		mood shifts, including depression; changes in libido				
lervous ystem	Headaches (including	nervousness, stupor, dizziness				

ystem Organ Class	frequency of undesirable effects					
	very common	**common**	**uncommon**	**Rare**	**very rare**	**not known**
isorders	migraines)					
ye disorders				incompati-bility with contact lenses		
astro-ntestinal isorders		nausea, vomiting, abdominal pain	abdominal cramps and bloating; diarrhoea			
epato-biliary isorders				cholestatic jaundice		
kin and sub-utaneous ssue disorders		acne	rash, chloasma (meliasma) possibly persistent, hirsutism, alopecia; urticaria	erythema nodosum	erythema multiforme	
eproductive ystem and reast disorders	Spotting, breakthrough bleeding	breast pain, sensitivity of the breasts, breast enlargement, mammary gland secretion, dysmenorrhoea, changes in the menstruation flow, changes on the cervix and in cervical secretion, amenorrhoea				
eneral isorders and dministration te conditions		fluid retention/ oedema				
ascular isorders				VTE ATE		
nvestigations		changes in weight (increase or decrease)	increased blood pressure, changes in the blood lipid levels, including hyper-triglyceri-daemia	Decreased serum folic acid level (serum folic acid levels can be decreased by COC therapy. In the event of a pregnancy that occurs shortly after discontinuation of the oral contraceptive, decreased serum folic acid levels may be of clinical relevance.)		

Furthermore, the following adverse events have been reported with the use of COCs. The frequency of the adverse reactions cannot be calculated from the reports.

- optic nerve inflammation (can result in partial or complete loss of vision), thrombosis of the retinal vessels
- Exacerbation of varicose veins
- pancreatitis with simultaneous severe hypertriglyceridemia

- ischemic colitis
- liver damage (e.g. hepatitis, liver dysfunction)
- gallbladder disease, including gallstones (COCs can result in the occurrence of a gallbladder disorder or exacerbate an existing gallbladder disease)
- haemolytic-uraemic syndrome
- gestational herpes
- otosclerosis
- exacerbation of systemic lupus erythematodes
- exacerbation of porphyria
- exacerbation of Sydenham's chorea
- exacerbation of depression
- chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis)
- Endometriosis, uterine fibroid
- Epilepsy

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 professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations
ATC-Code: G03AA07

Clinical studies have been conducted with another combined oral contraceptive containing Ethinylestradiol/Levonorgestrel 20 micrograms/100 micrograms in a total of 2,498 women in the age range 18 – 40 years. The Pearl Index calculated on the basis of these studies was approximately 0,69 (95% confidence interval: 0,30 – 1,36) based on a total of 15,026 cycles."

Mechanism of action:

The contraceptive effect of Elevin is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the endometrium.

5.2 Pharmacokinetic properties

Levonorgestrel

Absorption
Levonorgestrel is absorbed quickly and completely after oral administration and the maximum levonorgestrel serum concentrations of approximately 4.9 ng/ml are reached approximately 1-2 hours after taking it. Bioavailability is almost 101%.

Distribution
The serum levels of levonorgestrel drop two phases. The terminal phase is marked by a half-life of approximately 25 hours.
Levonorgestrel is linked to serum albumin and sexual hormone bonding globulin (SHBG). Only 1.1% of the total concentration of the medicinal product in the serum is a free steroid, approximately 65% is specifically linked to SHBG and approximately 35% is non-specifically linked to albumin. The increase in SHBG induced by ethinylestradiol influences the relative distribution of levonorgestrel in various protein fractions. The induction of the binding protein causes an increase in the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of levonorgestrel is 129 l after one dosage.

Biotransformation
Levonorgestrel is metabolised primarily by reduction on the Δ4-3-oxo-group and hydroxylation on positions 2α, 1β and 16β and then conjugation. The majority of metabolites circulating in the blood are sulphates of the 3α, 5β-tetrahydrolevonorgestrel, while it is primarily excreted in the form of glucuronides. A part of the unchanged levonorgestrel also circulates as 17β-sulphate. The metabolic clearance may vary interindividually by multiples and this might explain some of the great fluctuations observed in the levonorgestrel concentrations among users.

Elimination
Levonorgestrel and its metabolites are mostly eliminated with the urine (40%-68%) and approximately 16%-48% with the faeces.

Steady-state conditions
During continuous use of Elevin, the levonorgestrel serum levels increase approximately three-fold and reach steady-state during the second half of the treatment cycle. The pharmacokinetics of levonorgestrel are influenced by the SHBG serum level, which increase approximately 1.5-1.6-fold during administration of estradiol. Therefore, in steady-state, the serum clearance rate and the distribution volume are slightly reduced (0.7 ml/min/kg and approximately 100 l).

Ethinylestradiol

Absorption
Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of about 54,4pg/ml are reached within –the first 2 hours after tablet administration. During absorption and and first-pass liver metabolism, ethinylestradiol is comprehensively metabolised, resulting in a mean oral bioavailability of approximately 40-

45% (individual variation approximately 20-65%). Relative bioavailability compared to aqueous solution is 99%.

Distribution
The serum levels of ethinylestradiol decrease in two phases, which are characterised by half-lives of approximately 1 hour and 10 to 20 hours.
Ethinylestradiol is mainly (approximately 98%), but non-specifically bound to serum albumin and induces an increase in the serum concentrations of SHBG. The apparent distribution volume of ethinylestradiol is 2.8 - 8.6 l/kg.

Biotransformation
Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. . Ethinylestradiol is subject to enterohepatic circulation.

Elimination
Ethinylestradiol is not excreted in unchanged form. The metabolites are excreted via the urine and bile at a ratio of 4:6.

S*teady-state conditions*
During continuous use of Elevin, the ethinylestradiol serum concentration increases approximately two-fold. Due to the daily administration and the variable half-life in the terminal phase of serum clearance, steady-state is reached after approximately one week.

5.3 Preclinical safety data

The toxicity profile of ethinylestradiol and levonorgestrel is well known. The findings of animal experiments with oestrogens only have limited predicative value for using it on humans due to pronounced species differences. Ethinylestradiol showed an embryolethal effect in experimental animals at a relatively low dosage; malformations of the urogenital tract and feminisations of male foetuses have been observed; levonorgestrel showed an embryolethal effect in animal experiments and virilising effect on female foetuses at high dosages. Reproduction toxicological studies in rats, mice and rabbits did not bring about any indication of a teratogenic effect. Preclinical data for ethinylestradiol and levonorgestrel from conventional studies on chronic toxicity, genotoxicity and carcinogenic potential do not indicate any relevant risks for humans with the exception of those already described in the other sections of the summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
lactose monohydrate
maize starch
gelatin

magnesium stearate

Tablet coating:
hypromellose (3 cps)
Macrogol 4000
titanium dioxide (E171)
iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/PVDC aluminium blister packs or PP/COC/PP aluminium packs with 21 film-coated tablets (calendar packs).

Pack sizes:
21 film-coated tablets
3 x 21 film-coated tablets
6 x 21 film-coated tablets
13 x 21 film-coated tablets
100 x 21 film-coated tablets (hospital pack)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused product should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited
11 Boumpoulinas, Nicosia
1060 Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0289

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/03/2010

10 DATE OF REVISION OF THE TEXT

27/09/2024