PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed according to a doctor's prescription only

Angeliq®

Film-coated Tablets

Each film-coated tablet contains:
Estradiol (as hemihydrate) 1 mg,
Drospirenone 2 mg

Inactive ingredients and allergens in the preparation: see section 2 "Important information regarding some of the ingredients of the medicine and section 6 "Further Information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

1) WHAT IS THE MEDICINE INTENDED FOR?

Angeliq is a hormone replacement therapy (HRT) for use in postmenopausal women, whose last natural period was more than 12 months ago.

Angeliq is intended for –

- **Relief of symptoms occurring after menopause**
  During menopause, the amount of estrogen produced by the woman's body decreases. This effect may cause symptoms such as: hot flushes in the face, neck or chest. Angeliq alleviates these symptoms after menopause. The doctor will prescribe Angeliq for you only if the symptoms seriously hinder your daily life.
- **Prevention of osteoporosis**
  After menopause, some women may develop osteoporosis. Consult your doctor regarding treatment options. If you are at increased risk of developing osteoporosis fractures after menopause, and other medicines are not suitable for you, Angeliq can be used for preventing osteoporosis after menopause.

Therapeutic group: Angeliq belongs to a group of hormone replacement therapy medicines. The medicine contains two types of female hormones: estrogen and progestogen.

2) BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to estrogen, progestogen, or to any of the additional ingredients contained in the medicine. For a list of the inactive ingredients, see section 6 "Further Information".
- You are suspected of having, or you have or have had breast cancer.
- You are suspected of having, or you have estrogen-sensitive cancerous tumors, such as cancer of the womb lining.
- You have unexplained vaginal bleeding.
- You have excessive thickening of the womb lining (endometrial hyperplasia).
- You have or have ever had a blood clot in the vein (thrombosis), for example, in the veins of the legs (deep venous thrombosis) or the lungs (pulmonary embolism).
- You have a blood clotting disorder (such as protein C, protein S or antithrombin deficiency).
- You have or have recently had a disease caused by a blood clot in the arteries, such as a heart attack, stroke or angina pectoris.
- You have or have ever had a liver disease and your liver function test results have not yet returned to normal.
- You have a rare genetic blood problem called "porphyria".
- You have a severe kidney disease or acute kidney failure.
- You have reason to believe that you are pregnant or that you may be pregnant, or if you are producing breast milk or are breastfeeding (see "Pregnancy and breastfeeding" in section 2).

Do not take Angeliq if any of the above conditions are associated with you. If you are not sure regarding one of these instances, consult your doctor before taking Angeliq.

If any of the above conditions occur for the first time while taking Angeliq, stop taking the medicine at once, and consult the doctor immediately.

Special warnings regarding use of the medicine

Before taking Angeliq, talk to the doctor or pharmacist.

Before treatment with Angeliq, tell the doctor if any of the following conditions apply to you or if any of the following conditions develop, worsen or recur during treatment. In such a case, you will have to be checked by your doctor more often

- Myomas (fibroids) inside the womb.
- Growth of the womb lining outside the womb cavity (endometriosis) or a history of excessive thickening of the womb lining (endometrial hyperplasia).
- Increased risk of developing blood clots [see "Blood clots in the veins (thrombosis)" in section 2].
- Increased risk of getting an estrogen-sensitive cancer (such as a mother, sister or grandmother who had breast cancer).
- Hypertension.
- A liver disorder, such as a benign liver tumor.
- Diabetes.
- Gallstones.
- Migraine or severe headaches.
- A disease of the immune system that affects many organs of the body – systemic lupus erythematosus (SLE).
- Epilepsy.
- Asthma.
- A disease affecting the eardrum and hearing (otosclerosis).
- Very high levels of fats in the blood (triglycerides).
- Fluid retention due to cardiac or kidney problems.
- Hereditary or acquired angioedema.

Stop taking Angeliq and refer to a doctor immediately:

- If any of the conditions in section 2 "Do not use the medicine if" exist.
- If you notice yellowing of the skin or the whites of the eyes (jaundice). These may be signs of a liver disease.
- If you notice swelling in the face, tongue and/or throat and/or difficulty swallowing or hives, together with difficulty breathing which are suggestive of angioedema.
- If there is a large rise in your blood pressure (possible symptoms: headache, tiredness, dizziness).
- If you get migraine-like headaches for the first time.
- If you become pregnant.
- If you notice signs of a blood clot, such as:
  - painful swelling and redness of the legs
  - sudden chest pain
  - breathing difficulties

[see "Blood clots in the veins (thrombosis)" in section 2].

Angeliq is not a contraceptive. If less than 12 months have passed since your last period, or if you are below the age of 50, you may need to use an additional contraceptive to prevent pregnancy. Consult your doctor.

Medical history and regular check-ups

- The use of HRT carries risks which need to be considered when deciding whether to start treatment or whether to continue it.
- The experience in treating women with premature menopause (due to ovarian failure or surgery) is limited. If you have a premature menopause, the risks of using HRT may be different. Consult the doctor.
- Before you start (or restart) HRT, your doctor will ask you about your own and your family's medical history. The doctor may decide to perform physical examinations, e.g., breast examination and/or internal examinations, if necessary.
- Once you have started treatment with Angeliq, you should see your doctor for regular check-ups (at least once a year). At these check-ups, consult the doctor regarding the benefits and risks of continuing treatment with Angeliq.
- **Be sure to have routine breast exams as recommended by your doctor.**

See further information in section 2 "Additional conditions".

Hormone replacement therapy and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and endometrial cancer: Use of estrogens only increases the risk of getting endometrial cancer and of endometrial hyperplasia. The progestogen found in Angeliq protects you from this extra risk.

Irregular bleeding

You may have irregular bleeding or spotting during the first 3-6 months of taking Angeliq.

Refer to a doctor as soon as possible if:

- The bleeding carries on for more than the first 6 months.
- The bleeding starts after you have already been taking Angeliq for more than 6 months.
- The bleeding continues even after you have stopped taking Angeliq.

In these cases, consult with the doctor as soon as possible.

Breast cancer

Women who have breast cancer or have had the disease in the past should not use HRT.

Research shows that taking combined estrogen-progestogen or estrogen-only hormone replacement therapy (HRT) increases the risk of getting breast cancer. This extra risk depends on the duration of treatment. The additional risk becomes clear within 3 years of treatment. After stopping HRT, the extra risk will decrease with time. However, the excess risk may persist for 10 years or more if you have used HRT for more than 5 years.

Of 1,000 women aged 50 to 54 who are not taking HRT, on average, 13 to 17 women will be diagnosed with breast cancer over a 5-year period.
Of 1,000 women aged 50 who start taking estrogen-only HRT for 5 years, 16-17 women will be diagnosed with breast cancer (i.e., an extra 0 to 3 cases).
Of 1,000 women aged 50 who start taking estrogen-progestogen HRT for 5 years, 21 women will be diagnosed with breast cancer (i.e., an extra 4 to 8 cases).
Of 1,000 women aged 50 to 59 who are not taking HRT, on average, 27 women will be diagnosed with breast cancer over a 10-year period.
Of 1,000 women aged 50 who start taking estrogen-only HRT for 10 years, 34 cases will be diagnosed (i.e., an extra 7 cases).
Of 1,000 women aged 50 who start taking estrogen-progestogen HRT for 10 years, 48 cases will be diagnosed (i.e., an extra 21 cases).

Regularly check your breasts. Refer to the doctor if you notice any changes in the breast, such as:

- Sinking or dimpling of the skin.
- Changes in the nipple.
- Any lumps you can see or feel.

In addition, it is recommended that you join mammography screening programs (breast X-rays) when offered to you. When you undergo mammogram examination, it is important that you inform the nurse or healthcare professional who is performing the X-ray that you use HRT. This is because the treatment may increase the density of your breasts, which may affect the outcome of the test. If the density of the breast is increased, mammography may not detect all lumps.

Ovarian cancer

Ovarian cancer is rare – much rarer than breast cancer. The use of combined HRT (containing estrogen and progestogen) or HRT containing estrogen only has been associated with a slightly increased risk of ovarian cancer.

The risk of getting ovarian cancer varies with age. For example: of 2,000 women aged 50-54 who are not taking HRT, on average, about 2 women will be diagnosed with ovarian cancer over a 5-year period.
Of 2,000 women who have been taking HRT for 5 years, there will be about 3 cases of ovarian cancer (i.e., about one extra case).

The effects of HRT on the heart or blood circulation

Blood clots in the veins (thrombosis)

The risk of blood clots in the veins (deep vein thrombosis) is 1.3-3 times higher in women taking HRT when compared to women who are not taking it, especially during the first year of taking it.

Blood clots can be serious if they travel to the lungs, which can cause chest pain, breathlessness, fainting or even death.

The risk of blood clots in the veins increases with age and with the following risk factors. Inform the doctor if any of these situations is associated with you:

- If you are unable to walk for a long time because of major surgery, injury or illness (see "If you are due to undergo surgery" in section 3).
- If you are seriously overweight (BMI >30 kg/m^2).
- If you have a blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots.
- If any of your relatives has had blood clots in the legs, lungs or in any other organ.
- If you have systemic lupus erythematosus (SLE).
- If you have cancer.

Signs of a blood clot are detailed in section 2 "Stop taking Angeliq and refer to a doctor immediately".

Of 1,000 women in their 50s who are not taking HRT, on average, 4-7 women are expected to get a blood clot in a vein over a 5-year period.
Of 1,000 women in their 50s who are taking estrogen-progestogen HRT, on average, 9-12 women are expected to get a blood clot in a vein over a 5-year period (i.e., an extra 5 cases).

Heart disease (heart attack)

There is no evidence that HRT will prevent a heart attack.

Women over the age of 60 who are taking estrogen-progestogen HRT are at a slightly higher risk of developing heart disease in comparison to those who are not taking HRT.

Stroke

The risk of stroke is 1.5 times higher in women taking HRT than in women not taking it.

The number of extra cases of stroke due to use of HRT will increase with age.

Of 1,000 women in their 50s who are not taking HRT, on average, 8 women are expected to have a stroke over a 5-year period.
Of 1,000 women in their 50s who are taking HRT, on average, 11 women are expected to have a stroke over a 5-year period (i.e., an extra 3 cases).

Other conditions

- HRT will not prevent memory loss. There is evidence of a higher risk of memory loss in women who start taking HRT after the age of 65. Consult the doctor.
- If you have a kidney problem, and have high potassium levels in the blood, particularly if you are taking other medicines that increase the amount of potassium in the blood, your doctor may check the potassium level in your blood during the first month of treatment.
- If you have high blood pressure, treatment with Angeliq may decrease blood pressure. Do not use Angeliq as treatment for high blood pressure.
- If you have a tendency to develop golden-brown patches on the face (chloasma), you should avoid exposure to the sun or to ultraviolet radiation during the course of treatment with Angeliq.

Drug interactions:

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.

Some medicines may interfere with the effect of Angeliq and lead to irregular bleeding. These medicines include:

- Medicines to treat epilepsy (e.g., barbiturates, phenytoin, primidone, carbamazepine, oxcarbazepine, topiramate and felbamate).
- Medicines to treat tuberculosis (e.g., rifampicin, rifabutin).
- Medicines to treat infections by the AIDS virus (HIV) and to treat hepatitis C virus infections (called protease inhibitors and non-nucleoside reverse transcriptase inhibitors, e.g., nevirapine, efavirenz, nelfinavir, ritonavir).
- The herbal preparation St. John's wort (*Hypericum perforatum*).
- Medicines to treat hepatitis C virus (HCV) (such as combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir as well as glecaprevir/pibrentasvir) may cause increases in liver function blood test results (increase in ALT liver enzyme) in women using CHCs containing ethinylestradiol. Angeliq contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme may occur when using Angeliq with this HCV combination regimen. Your doctor will advise you about that.
- Medicines to treat fungal infections (e.g., griseofulvin, itraconazole, ketoconazole, voriconazole, fluconazole).
- Medicines to treat bacterial infections (e.g., clarithromycin, erythromycin).
- Medicines for treatment of certain heart diseases or high blood pressure (verapamil, diltiazem).
- Grapefruit juice.

The following medicines may cause a small increase in potassium levels in the blood:

- Medicines for the treatment of inflammation or pain (e.g., aspirin and ibuprofen).
- Certain types of medicines to treat heart diseases or high blood pressure (diuretics, ACE inhibitors, e.g., enalapril, angiotensin II receptor antagonists, e.g., losartan). When using medicines for treatment of high blood pressure in combination with Angeliq, there may be an additional decrease in blood pressure.

Smoking

Smoking is a risk factor for stroke in women taking HRT (see "Stroke" in section 2).

Use of the medicine and food

This medicine can be taken with or without food.

Use of the medicine and alcohol consumption

Excessive alcohol drinking is a risk factor for stroke in women taking HRT (see "Stroke" in section 2).

Laboratory tests

If you perform blood tests, tell the doctor or the laboratory staff that you are taking Angeliq, since this medicine may influence the results of certain tests.

Pregnancy and breastfeeding

Angeliq is intended for postmenopausal women. If you become pregnant, stop taking the medicine immediately and refer to the doctor.

Angeliq is not intended for use during breastfeeding.

Driving and use of machines

There is no evidence that use of Angeliq influences driving or use of machines.

Important information regarding some of the ingredients of the medicine

The medicine contains lactose (a type of sugar). If you have been told by the doctor that you suffer from intolerance to any sugars, consult the doctor before taking the medicine.

3) HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain regarding the dosage and treatment regimen of the preparation.

- Do not start taking Angeliq before at least 12 months have passed since your last natural period.

The dosage and treatment regimen will be determined by the doctor only. The usual dosage is generally to take one whole tablet, every day, at a set time, for 28 days.

Do not exceed the recommended dose.

- The day of the week and an arrow pointing you in the direction of progression are marked on the pack. The doctor will instruct you when to start taking the tablets (see in "When can you start using the first pack?" section).
- On the day you start the pack, take the tablet from the top row, marked with the correct day of the week. For example: "TUE" – indicates Tuesday.
- Take one tablet every day, according to the direction of the arrows, until you have finished the 28 tablets in the pack.
- When you finish the pack, start a new pack immediately. There is no break between taking one pack and the next. It is recommended to take the tablet at a set time every day.

When can you start using the first pack?

- If you are taking another HRT: continue taking the current pack until you finish it. Take the first Angeliq tablet the day after finishing the pack. Do not take a break between the previous kind of tablets and Angeliq.
- If this is your first HRT: you can start taking Angeliq on any day you wish.

Method of administration

Swallow the tablet whole with a glass of water or milk.

There is no information regarding crushing/halving/chewing.

If you accidentally took a higher dosage

Overdose may cause nausea, vomiting or irregular bleeding. There is no specific treatment necessary, but if you are worried, consult a doctor.

If a child accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of this medicine with you.

If you forgot to take Angeliq

- If you forgot to take an Angeliq tablet at the set time and the delay in taking the tablet is less than 24 hours, take the tablet as quickly as possible and continue taking the rest of the tablets as usual, in the direction of the arrow, at your set time.
- If the delay in taking the tablet exceeds 24 hours, leave the forgotten tablet in the pack and continue taking the rest of the tablets as usual, in the direction of the arrow, at your set time. Do not take a double dose to compensate for the forgotten dose.
- If you forgot to take the tablets for a few days, irregular bleeding may occur.

If you stop taking Angeliq

You may begin to feel the usual symptoms of menopause again, which may include hot flushes, sleeping problems, nervousness, dizziness or vaginal dryness. You will may also lose bone mass when you stop taking Angeliq. Consult your doctor or pharmacist if you want to stop taking Angeliq. If you have further questions on the use of this medicine, consult your doctor or pharmacist.

If you are due to undergo surgery

Tell your surgeon that you are taking Angeliq. You may need to stop taking Angeliq about 4-6 weeks before the surgery, to reduce the risk of a blood clot [see "Blood clots in the veins (thrombosis)" in section 2]. Consult the doctor about when you can resume taking Angeliq.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4) SIDE EFFECTS

As with any medicine, use of Angeliq may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Woman taking HRT report the following diseases more often than women who are not taking HRT:

Severe side effects

- Breast cancer
- Excessive thickening of the lining of the womb (endometrial hyperplasia) or endometrial cancer
- Ovarian cancer
- Blood clots in the veins of the leg or the lungs (venous thrombosis or pulmonary embolism)
- Heart disease
- Stroke
- Possible memory loss if treatment is started over the age of 65

For additional information on these side effects, see section 2 "Before Using the Medicine".

Additional side effects

The following side effects have been associated with use of Angeliq:

Very common side effects – effects that occur in more than 1 in 10 users:

- Unexpected menstruation-like bleeding (see in section 2 "HRT and cancer")
- Breast tenderness
- Breast pains

Unexpected menstruation-like bleeding occurs during the first few months of treatment with the medicine. It is usually temporary and normally disappears with continued treatment. If it does not, refer to the doctor.

Common side effects – effects that occur in 1-10 users in 100:

- Depression, mood changes, nervousness
- Headaches
- Stomachaches, nausea, stomach enlargement
- Benign breast tumors, swollen breasts
- Increase in size of uterine fibroids
- Non-cancerous growths in the cervix (benign cervical growths)
- Irregularities in your vaginal bleeding
- Vaginal discharge
- Loss of energy
- Localized fluid retention

Uncommon side effects – effects that occur in 1-10 users in 1,000:

- Weight gain/loss, increased/loss of appetite, increased blood fats
- Sleep problems, anxiety, decrease in sex drive
- Burning or pricking sensation, decreased concentration, dizziness
- Eye problems (e.g., red eyes), visual disturbances (e.g., blurred vision)
- Palpitations
- Blood clot, venous thrombosis [leg pain, also see in section 2 "Blood clots in a vein (thrombosis)"], high blood pressure, migraine, inflammation of the veins, varicose veins
- Breathlessness
- Stomach disorder, diarrhea, constipation, vomiting, dry mouth, wind, altered sense of taste
- Altered levels of liver enzymes (will show up in a blood test)
- Skin problems, acne, hair loss, skin itchiness, excessive hairiness
- Backache, joint pain, pain in limbs, muscle cramps
- Urinary tract inflammation and disorders
- Breast cancer, thickening of the lining of the womb, benign unusual growths in the uterus, thrush, vaginal dryness and itching or vaginal burning
- Lumpy breasts (fibrocystic), disorders of the ovaries, cervix and uterus, pelvic pain
- Generalized fluid retention, chest pain, general unwell feeling, increase in sweating

Rare side effects – effects that occur in 1-10 users in 10,000:

- Anemia
- Vertigo (spinning sensation)
- Ringing in the ears (tinnitus)
- Gallstones
- Muscle pains (myalgia)
- Inflammation of the fallopian tubes
- Milk discharge from the nipples (galactorrhea)
- Chills

The following side effects have been observed in clinical trials of women with high blood pressure:

- High blood potassium levels (hyperkalemia) sometimes causing muscle cramps, diarrhea, nausea, dizziness or headaches
- Heart failure, enlargement of the heart, heart rhythm disorders (atrial flutter), an effect on heart rhythm
- Increase in level of blood aldosterone

The following side effects have been observed in other types of HRTs:

- Gallbladder disease
- Various skin disorders:
  - Discoloration of the skin, especially of the face or neck, known as "pregnancy patches" (chloasma)
  - Reddish and painful skin nodules (erythema nodosum)
  - Rash with target-shaped reddening or sores (erythema multiforme)

If a side effects occurs, if one of the side effects worsens, or if you are suffering from a side effect not mentioned in the leaflet, consult with the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

5) HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine must be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- Do not store at a temperature that exceeds 25°C.
- Do not discard medicines in the wastewater or household waste bin. Consult the pharmacist as to how to dispose of medicines you no longer use. These measures will help protect the environment.

6) FURTHER INFORMATION

- In addition to the active ingredients, the medicine also contains:
  Lactose monohydrate, Maize starch, Starch pregelatinized, Povidone, Magnesium stearate, Hypromellose 5cP, Macrogol 6000, Talc, Titanium dioxide (E-171), Ferric oxide red (E-172).
- Each tablet contains 48.2 mg lactose monohydrate.
- What the medicine looks like and the contents of the package:
  Angeliq film-coated tablets are round, red, biconvex, marked with "DL" in a hexagon on one side.
  The tablets are provided in trays (blisters) in packs of 28 or 3x28 tablets.
- Registration Holder and Address: Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240.
- Name of Manufacturer and Address: Bayer AG, Berlin, Germany.
- Revised in June 2022 according to MOH guidelines.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health: 132 92 31057 00.

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