Package leaflet: Information for the user

Cliovelle 1 mg/0.5 mg tablets

Estradiol/Norethisterone Acetate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cliovelle is and what it is used for

Cliovelle is a Hormone Replacement Therapy (HRT). It contains two types of female hormones, an oestrogen and a progestogen. Cliovelle is used in postmenopausal women with at least 1 year since their last natural period.

Cliovelle is used for:

Relief of symptoms occurring after menopause
During the menopause, the amount of oestrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ("hot flushes"). Cliovelle alleviates these symptoms after menopause. You will only be prescribed Cliovelle if your symptoms seriously hinder your daily life.

Prevention of osteoporosis
After the menopause some women may develop fragile bones (osteoporosis). You should discuss all available options with your doctor.
If you are at an increased risk of fractures due to osteoporosis and other medicines are not suitable for you, you can use Cliovelle to prevent osteoporosis after menopause.

2. What you need to know before you take Cliovelle

Medical history and regular check-ups
The use of HRT carries risks which need to be considered when deciding whether to start taking it, or whether to carry on taking it.

The experience in treating women with a premature menopause (due to ovarian failure or surgery) is limited. If you have a premature menopause the risks of using HRT may be different. Please talk to your doctor.

Before you start (or restart) HRT, your doctor will ask about your own and your family's medical history. Your doctor may decide to perform a physical examination. This may include an examination of your breasts and/or an internal examination, if necessary.

Once you have started on Cliovelle you should see your doctor for regular check-ups (at least once a year). At these check-ups, discuss with your doctor the benefits and risks of continuing with Cliovelle.

Go for regular breast screening, as recommended by your doctor.

Do not take Cliovelle
if any of the following applies to you. If you are not sure about any of the points below, **talk to your doctor** before taking Cliovelle.

Do not take Cliovelle if you
- have or have ever had **breast cancer**, or if you are suspected of having it;
- have **cancer which is sensitive to oestrogens**, such as cancer of the womb lining (endometrium), or if you are suspected of having it;
- have any **unexplained vaginal bleeding**;
- have **excessive thickening of the womb lining** (endometrial hyperplasia) that is not being treated;
- have or have ever had a **blood clot in a vein** (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism);
- have a **blood clotting disorder** (such as protein C, protein S, or antithrombin deficiency);
- have or recently have had a disease caused by blood clots in the arteries, such as **heart attack, stroke** or **angina**;
- have or have ever had a **liver disease** and your liver function tests have not returned to normal;
- have a rare blood problem called “porphyria” which is passed down in families (inherited);
- are **allergic** to estradiol valerate, norethisterone acetate or any of the other ingredients of this medicine (listed in section 6).

If any of the above conditions appear for the first time while taking Cliovelle, stop taking it at once and consult your doctor immediately.

Warnings and precautions
Tell your doctor if you have ever had any of the following problems, before you start the treatment, as these may return or become worse during treatment with Cliovelle. If so, you should see your doctor more often for check-ups:
- fibroids inside your womb;
- growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia);
- increased risk of developing blood clots (see “Blood clots in a vein (thrombosis)”);
- increased risk of getting an oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer);
- high blood pressure;
- a liver disorder, such as a benign liver tumour;
- diabetes;
- gallstones;
- migraine or severe headaches;
- a disease of the immune systems that affects many organs of the body (systemic lupus erythematosus, SLE);
- epilepsy;
- asthma;
- a disease affecting the eardrum and hearing (otosclerosis);
- a very high level of fat in your blood (triglycerides);
- fluid retention due to cardiac and kidney problems;
- hereditary and acquired angioedema.

Stop taking Cliovelle and see a doctor immediately
if you notice any of the following when taking HRT:
- any of the conditions mentioned in the “Do not take Cliovelle “ section;

- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease.
- swollen face, tongue and/or throat and/or difficulty swallowing or hives, together with difficulty breathing which are suggestive of an angioedema;
- a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness);
- migraine-like headaches which happen 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,
  - difficulty in breathing.

  For more information, see "Blood clots in a vein (thrombosis)".

Note: Cliovelle is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Speak to your doctor for advice.

HRT and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)
Taking oestrogen-only HRT will increase the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer).
The progestogen in Cliovelle protects you from this extra risk.

Irregular bleeding
You may have irregular bleeding or drops of blood (spotting) during the first 3-6 months of taking Cliovelle. However, if the irregular bleeding:
- carries on for more than the first 6 months,
- starts after you have been taking Cliovelle for more than 6 months,
- carries on after you have stopped taking Cliovelle,

see your doctor as soon as possible.

Breast cancer
Evidence shows that taking combined oestrogen-progestogen or oestrogen-only hormone replacement therapy (HRT) increases the risk of breast cancer. The extra risk depends on how long you use HRT. The additional risk becomes clear within 3 years of use. After stopping HRT the extra risk will decrease with time, but the risk may persist for 10 years or more if you have used HRT for more than 5 years.

Compare
Women aged 50 to 54 who are not taking HRT, on average, 13 to 17 in 1000 will be diagnosed with breast cancer over a 5-year period.
For women aged 50 who start taking oestrogen-only HRT for 5 years, there will be 16-17 cases in 1000 users (i.e. an extra 0 to 3 cases).
For women aged 50 who start taking oestrogen-progestogen HRT for 5 years, there will be 21 cases in 1000 users (i.e. an extra 4 to 8 cases).

Women aged 50 to 59 who are not taking HRT, on average, 27 in 1000 will be diagnosed with breast cancer over a 10-year period.
For women aged 50 who start taking oestrogen-only HRT for 10 years, there will be 34 cases in 1000 users (i.e. an extra 7 cases).
For women aged 50 who start taking oestrogen-progestogen HRT for 10 years, there will be 48 cases in 1000 users (i.e. an extra 21 cases).

- **Regularly check your breasts. See your doctor if you notice any changes such as:**
  - dimpling of the skin;
  - changes in the nipple;
  - any lumps you can see or feel.

Additionally, you are advised to join mammography screening programs when offered to you. For mammogram screening, it is important that you inform the nurse/healthcare professional who is actually taking the x-ray that you use HRT, as this medication may increase the density of your breasts which may affect the outcome of the mammogram. Where 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 oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer.

The risk of ovarian cancer varies with age. For example, in women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be about 3 cases per 2000 users (i.e. about 1 extra case).

Effect of HRT on heart and circulation

Blood clots in a vein (thrombosis)
The risk of **blood clots in the veins** is about 1.3 to 3 times higher in HRT users than in non-users, especially during the first year of taking it.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death.

You are more likely to get a blood clot in your veins as you get older and if any of the following applies to you. Inform your doctor if any of these situations applies to you:
- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3 “If you need to have surgery”);
- you are seriously overweight (BMI > 30 kg/m^2);
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots;
- if any of your close relatives has ever had a blood clot in the leg, lung or another organ;
- you have systemic lupus erythematosus (SLE);
- you have cancer.

For signs of a blood clot, see “Stop taking Cliovelle and see a doctor immediately”.

Compare
Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1000 would be expected to get a blood clot in a vein.
For women in their 50s who have been taking oestrogen-progestogen HRT for over 5 years, there will be 9 to 12 cases in 1000 users (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 years who use oestrogen-progestogen HRT are slightly more likely to develop heart disease than those not taking any HRT.

Stroke
The risk of getting stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

Compare
Looking at women in their 50s who are not taking HRT, on average, 8 in 1000 would be expected to have a stroke over a 5-year period. For women in their 50s who are taking HRT, there will be 11 cases in 1000 users, over 5 years (i.e. an extra 3 cases).

Other conditions
HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Other medicines and Cliovelle
Some medicines may interfere with the effect of Cliovelle. This might lead to irregular bleeding. This applies to the following medicines:
- Medicines for **epilepsy** (such as phenobarbital, phenytoin and carbamazepine);
- Medicines for **tuberculosis** (such as rifampicin, rifabutin);
- Medicines for **HIV infection** (such as nevirapine, efavirenz, ritonavir, telaprevir and nelfinavir);
- Herbal remedies containing **St John's wort** (Hypericum perforatum).

HRT can affect the way some other medicines work:
- A medicine for epilepsy (lamotrigine), as this could increase frequency of seizures.
- The Hepatitis C virus (HCV) combination regimens ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir may cause increases in liver function blood test results (increase in ALT liver enzyme) in women using CHCs containing ethinylestradiol. Cliovelle contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Cliovelle with this HCV combination regimen. Your doctor will advise you.

Cliovelle can increase or decrease the effects of other medicinal products:
- The effect of cyclosporine (e.g. used for prevention of transplant rejection, treatment of symptoms of rheumatoid arthritis or psoriasis) may be increased.

Medicinal products which contain ketoconazole (an antifungal) can increase the effect of Cliovelle.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription, herbal medicines or other natural products. Your doctor will advise you.

Laboratory tests
If you need a blood test, tell your doctor or the laboratory staff that you are taking Cliovelle, because this medicine can affect the results of some tests.

Pregnancy and breast-feeding
Cliovelle is for use in postmenopausal women only. If you become pregnant, stop taking Cliovelle and contact your doctor.

Driving and using machines
No effects on the ability to drive vehicles and use machines have been observed.

Cliovelle contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Cliovelle

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Take one tablet a day without a break between tablet cards (blister packs).

The first tablet is removed and taken from the blister indicated by the day of the week when you start taking Cliovelle (e.g. “Mon” for Monday). One further tablet is then removed each day in the direction of the arrow, until the blister is finished. Start a new blister the next day.

The tablets must be swallowed with an adequate quantity of water, preferably at the same time each day.

Your doctor will aim to prescribe the lowest dose to treat your symptoms for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

If you take more Cliovelle than you should
If you have taken too much of the medicinal product, contact your doctor or hospital to assess the risk and for advice.

Following an overdose you may experience breast tenderness, feel sick (nauseous), must vomit, have irregular periods, feel down, feel tired, develop acne or experience an increase in body and facial hair.

If you have taken an extra dose by mistake, the usual dose should nevertheless be taken on the next day.

If you forget to take Cliovelle
If you forgot to take a tablet you can take it within 12 hours of the usual time, otherwise you must discard the forgotten tablet and take the next tablet as usual on the next day.

Do not take a double dose to make up for a forgotten tablet.

If you need to have surgery
If you are going to have surgery, tell the surgeon that you are taking Cliovelle. You may need to stop taking Cliovelle about 4 to 6 weeks before the operation to reduce the risk of a blood clot (see section 2 “Blood clots in a vein (thrombosis)”). Ask your doctor when you can start taking Cliovelle again.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the side effects are mild to moderate and do not mean that women have to stop taking their tablets.

The following diseases are reported more often in women using HRT compared to women not using HRT:
- breast cancer;
- abnormal growth or cancer of the lining of the womb (endometrial hyperplasia or cancer);
- ovarian cancer;
- blood clots in the veins of the legs or lungs (venous thromboembolism);
- heart disease;
- stroke;
- probable memory loss if HRT is started over the age of 65.

For more information about these side effects, see section 2.

The following side effects can occur during treatment with Cliovelle:

Very common (may affect more than 1 in 10 users)
Vaginal bleeding. Pain or tenderness in the breasts.

Common (may affect up to 1 in 10 users)
Fungal infections in the genital area or vaginal inflammation. Accumulation of fluid in the body. Depression or worsening of existing depression. Migraine or worsening of existing migraine, headache. Nausea. Back pain. Breast oedema or breast enlargement. Uterine tumours (myoma) or aggravated or recurrent uterine tumours. Peripheral oedema (swollen arms and legs). Weight gain.

Uncommon (may affect up to 1 in 100 users)
Hypersensitivity (allergic reaction). Nervousness. Superficial vein inflammation combined with blood clots. Pains, feelings of tightness or discomfort in the abdomen. Gases, bloating. Morbidly increased hirsutism (increased hair growth on the body and face), acne, hair loss. Itching. Nettle rash. Cramps in the legs.

Rare (may affect up to 1 in 1,000 users)
Blood clots in the lungs (see also section 2 “What you need to know before you take Cliovelle”). Deep vein inflammation combined with blood clots.

Very rare (may affect up to 1 in 10,000 users)
Anaphylactic reactions (sudden, severe, potentially life-threatening allergic reactions).

The following side effects have been reported with other HRTs:
- gall bladder disease;
- various skin disorders:
  - discolouration of the skin especially of the face or neck known as “pregnancy patches” (chloasma),
  - painful reddish skin nodules (erythema nodosum),
  - rash with target-shaped reddening or sores (erythema multiforme);
- dry eyes;
- tear film composition changes.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cliovelle

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and on the carton after “EXP”. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater <or household waste>. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cliovelle contains
- The active substances are estradiol 1 mg (as estradiol valerate) and norethisterone acetate 0.5 mg.

- The other ingredients are copovidone, lactose monohydrate, magnesium stearate and maize starch.

What Cliovelle looks like and contents of the pack
White, round, biconvex tablets 6 mm in diameter.
Calendar blister packs of 28 and 84 tablets.
Blister packs of 30 and 90 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
[To be completed nationally]

This medicine is authorised in the Member States of the European Economic Area under the following names:
<{Name of the Member State}> <{Name of the medicine}>
<{Name of the Member State}> <{Name of the medicine}>

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Other sources of information
Detailed information on this medicine is available on the website of {name of Member State Agency (link)}