

Note: Indivina 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 Indivina 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 Indivina. However, if the irregular bleeding:

- carries on for more than the first 6 months
- starts after you have been taking Indivina for more than 6 months
- carries on after you have stopped taking Indivina

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 2,000 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 2,000 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/m²)
- 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 Indivina 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 1,000 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 1,000 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 a 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 1,000 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 1,000 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.
- If you are taking thyroid hormone replacement therapy (e.g. thyroxine), your doctor may monitor your thyroid function more often when you start treatment.
- If you have or have had cholasma (yellowish-brown pigmentation patches on the skin, particularly of the face); if so, minimize your exposure to the sun or ultraviolet radiation whilst using Indivina.

Other medicines and Indivina

Some medicines may interfere with the effect of Indivina. This might lead to irregular bleeding. This applies to the following medicines:

- Medicines for **epilepsy** (such as phenobarbital, phenytoin and carbamazepin)
- Medicines for **tuberculosis** (such as rifampicin, rifabutin)
- Medicines for **HIV infection** (such as nevirapine, efavirenz, ritonavir and nelfinavir)
- Herbal remedies containing **St John’s Wort** (*Hypericum perforatum*)
- Medicines for Hepatitis C virus (HCV) (such as combination regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir as well as a regimen with glecaprevir/pibrentasvir) may cause increases in liver function blood test results (increase in ALT liver enzyme) in women using CHCs containing ethinylestradiol. Indivina contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Indivina with this HCV combination regimen. Your doctor will advise you.

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.

Laboratory tests

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

Pregnancy and breast-feeding

Indivina is for use in postmenopausal women only. If you become pregnant, stop taking Indivina and contact your doctor.

Driving and using machines

Indivina has no influence on your ability to drive or use machines.

Indivina contains lactose

This medicine contains 78.9 mg (1 mg/2.5 mg tablet), 76.5 mg (1 mg/5 mg tablet) or 75.5 mg (2 mg/5 mg tablet) lactose (as monohydrate). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Indivina

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Your doctor will aim to prescribe the lowest dose to treat your symptom for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

Take one Indivina tablet every day, preferably at about the same time each day. Calendar days are printed on the blister sheet to help you follow your daily tablet intake. Swallow the tablet whole with a drink. You will normally start on the lowest dose of Indivina and this will be increased, if necessary. Your doctor should aim to prescribe the lowest dose for the shortest time that gives you relief from your symptoms. Talk to your doctor if your symptoms are not better after three months. If you feel that the effect of Indivina is too strong or too weak, do not change the dose or stop taking the tablets yourself, but ask your doctor for advice.

If you are not having periods and you have not previously taken HRT or you are changing from another continuous combined HRT product, treatment with Indivina may be started on any day.

If you switch from a cyclic HRT regimen, start Indivina treatment one week after taking the last tablet of the cyclic HRT. Talk to your doctor or pharmacist if you are unsure.

Whilst taking this medicine

When you first start taking Indivina you may get some bleeding at odd times for a few months (Please also refer to the section above on Endometrial cancer). However, if this is still happening after a few months or if you experience heavy bleeding tell your doctor.

If you take more Indivina than you should

If you or somebody else has taken too many Indivina tablets, talk to your doctor or pharmacist. An overdose of Indivina could make you feel sick, or make you get a headache or uterine bleeding.

If you forget to take Indivina

It is best to take the tablet at the same time each day. Do not take a double dose to make up for a forgotten tablet. You should then continue by taking the next tablet at your usual time. Missing a tablet or irregular use of Indivina tablets may cause breakthrough bleeding or spotting.

If you stop taking Indivina

If you want to stop taking Indivina, talk to your doctor first. He/she will explain the effects of stopping treatment and discuss other possibilities with you.

If you need to have surgery

If you are going to have surgery, tell the surgeon that you are taking Indivina. You may need to stop using Indivina about 4 to 6 weeks before the operation to reduce the risk of a blood clot (see section 2, Blood clots in a vein). Ask your doctor when you can start using Indivina 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, particularly early on (in the first few months of treatment), for example irregular bleeding may occur, although not everybody gets them. These often disappear with continued treatment.

There are a number of situations in which you may have to **stop taking Indivina**. Tell your doctor immediately if you develop any of the following conditions:

- develop signs of jaundice (yellowing of the skin or the whites of the eyes)
- experience a migraine type headache for the first time
- become pregnant
- experience a significant increase in your blood pressure

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 is a list of side effects that have been linked to the use of HRT:

Common side effects (may affect up to 1 in 10 people):

- weight increase or decrease, swelling caused by fluid retention
- depression, nervousness, lack of energy
- headache, dizziness
- hot flushes, increased sweating
- feeling sick, vomiting, stomach cramps, gas
- breast tension and pain, vaginal discharge, bleeding or spotting, disorder of vulva/vagina, menstrual disorder.

Uncommon side effects (may affect up to 1 in 100 people):

- benign breast tumor, benign growths in the lining of the womb
- allergic (hypersensitivity) reaction
- increased appetite, high level of cholesterol in the blood
- anxiety, inability to sleep, apathy, mood swings, poor concentration, changes in sex drive or mood, euphoria, agitation
- migraine, sensation of tingling, prickling or numbness in skin, trembling
- visual impairment, dry eye
- feeling your heartbeat
- increased blood pressure, inflammation of a vein, purple patches like bruising
- breathlessness, runny or blocked nose
- constipation, indigestion/heartburn, diarrhea, rectal disorder
- acne, hair loss, dry skin, nail problems, skin nodule, excessive hair growth (hirsutism), painful reddish skin nodules (*erythema nodosum*), generalized itchy rash
- joint disorders, muscle cramps
- increased frequency or urge to pass urine, lack of bladder control, bladder infections, discoloured urine, blood in the urine
- breast enlargement, breast tenderness, thickening of the lining of the womb, uterine disorder
- tiredness, abnormal laboratory tests, weakness, fever, flu-like symptoms, feeling generally unwell.