

## **PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Indivina 1 mg/2.5 mg tablets**  
**Indivina 1 mg/5 mg tablets**  
**Indivina 2 mg/5 mg tablets**  
estradiol/medroxyprogesterone

### **Read all of this leaflet carefully before you start taking this medicine**

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### **In this leaflet:**

1. What Indivina is and what it is used for
2. Before you take Indivina
3. How to take Indivina
4. Possible side effects
5. How to store Indivina
6. Further information

## **1. WHAT INDIVINA IS AND WHAT IT IS USED FOR**

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

Indivina is used for:

### **Relief of symptoms occurring after menopause**

During the menopause, the amount of the oestrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ("hot flushes"). Indivina alleviates these symptoms after menopause. You will only be prescribed Indivina 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 Indivina to prevent osteoporosis after menopause.

## **2. BEFORE YOU TAKE INDIVINA**

### **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 Indivina 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 Indivina.

Go for regular breast screening as recommended by your doctor.

### **Do not take Indivina:**

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 Indivina.

Do not take Indivina

- if you have or have ever had **breast cancer**, or if you are suspected of having it
- if you have **cancer which is sensitive to oestrogens**, such as cancer of the womb lining (endometrium), or if you are suspected of having it
- if you have any **unexplained vaginal bleeding**
- if you have **excessive thickening of the womb lining** (endometrial hyperplasia) that is not being treated
- if you 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)
- if you have a **blood clotting disorder** (such as protein C, protein S, or antithrombin deficiency)
- if you have or recently have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke** or **angina**
- if you have or have ever had a **liver disease** and your liver function tests have not returned to normal
- if you have a rare blood problem called "porphyria" which is passed down in families (inherited)
- if you are **allergic** (hypersensitive) to **estradiol valerate** or **medroxyprogesterone acetate** or any of the other ingredients of Indivina (listed in section 6 Further information).

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

### **When to take special care with Indivina**

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 Indivina. 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 a 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 system 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 or kidney problems.

**Stop taking Indivina 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 Indivina” section
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease
- 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:** 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 suggests that taking combined oestrogen-progestogen and possibly also oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.

#### *Compare*

Women aged 50 to 79 who are not taking HRT, on average, 9 to 14 in 1,000 will be diagnosed with breast cancer over a 5-year period. For women aged 50 to 79 who are taking oestrogen-progestogen HRT over 5 years, there will be 13 to 20 cases in 1,000 users (i.e. an extra 4 to 6 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.

### **Ovarian cancer**

Ovarian cancer is rare. A slightly increased risk of ovarian cancer has been reported in women taking HRT for at least 5 to 10 years.

Women aged 50 to 69 who are not taking HRT, on average about 2 women in 1,000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be between 2 and 3 cases per 1,000 users (i.e. up to 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<sup>2</sup>)
- 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.

### **Taking other medicines**

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*).

Please tell your doctor or pharmacist if you are taking or have recently taken 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.

### **Taking Indivina with food and drink**

Indivina can be swallowed with a glass of water at the same time each day.

### **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.

### **Important information about some ingredients of Indivina**

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

## **3. HOW TO TAKE INDIVINA**

Always take Indivina as your doctor has told you. You should 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 if necessary. 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. If you forget to take a tablet leave the 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 have any further questions on the use of this product, ask your doctor or pharmacist.

#### **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.

## **4. POSSIBLE SIDE EFFECTS**

Like all medicines, Indivina may cause side effects although not everybody gets them, particularly early on (in the first few months of treatment), for example irregular bleeding may occur. 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.

## Other side effects

**Common** (affecting more than 1 person in 100):

- changes in mood including anxiety and depressive mood, changes in libido
- headache
- feeling sick, stomach pain
- breakthrough bleeding, increase in size of uterine muscle lumps (fibroids), breast tenderness, breast enlargement
- weight increase or decrease, swelling caused by fluid retention.

**Uncommon** (affecting more than 1 in 1,000 but less than 1 in 100)

- dizziness, migraine
- increased blood pressure
- indigestion/heartburn, vomiting, flatulence, gall bladder disease and/or gallstones
- vaginal thrush (candidiasis)
- leg cramps.

**Rare** (affecting more than 1 in 10,000 but less than 1 in 1,000)

- skin rash, itching
- blood clots
- hair loss, excessive hair growth (hirsutism).

The following side effects have been reported with other HRTs:

- gall bladder disease
- inflammation of pancreas (pancreatitis)
- 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*).

If you notice any side effects not listed in this leaflet or if any of the side effects mentioned gets serious please tell your doctor or pharmacist.

## 5. HOW TO STORE INDIVINA

Keep out of the reach and sight of children. Do not use Indivina after the expiry date which is stated on the pack. Store below 25°C. Store in the original package in order to protect from moisture. Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Indivina contains:

The active ingredients of Indivina tablets are estradiol valerate and medroxyprogesterone acetate. Three different strengths of tablets are available.

Indivina 1 mg/2.5 mg tablets contain 1 mg of estradiol valerate and 2.5 mg medroxyprogesterone acetate.

Indivina 1 mg/5 mg tablets contain 1 mg of estradiol valerate and 5 mg medroxyprogesterone acetate.

Indivina 2 mg/5 mg tablets contain 2 mg of estradiol valerate and 5 mg medroxyprogesterone acetate.

The other ingredients of all Indivina tablets are lactose monohydrate, maize starch, gelatin, and magnesium stearate.

**What Indivina looks like and contents of the pack:**

Indivina 1 mg/2.5 mg tablets are white, round, bevelled-edge, diameter 7 mm, flat tablets with a code '1 + 2.5' on one side.

Indivina 1 mg/5 mg tablets are white, round, bevelled-edge, diameter 7 mm, flat tablets with a code '1 + 5' on one side.

Indivina 2 mg/5 mg tablets are white, round, bevelled-edge, diameter 7 mm, flat tablets with a code '2 + 5' on one side.

The tablets are packed in a PVC/PVDC-aluminium blister of 28 tablets. The pack sizes available are 1 x 28 tablets and 3 x 28 tablets for all three strengths. All pack sizes may not be available in your country.

**Marketing Authorisation Holder:**

Orion Corporation  
Orionintie 1  
FI-02200 Espoo  
FINLAND

**Manufacturer:**

Orion Corporation  
Tengströminkatu 8  
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**This medicinal product is authorised in the Member States of the EEA under the following names:**

Indivina, Duova

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