

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ovaleap 300 IU/0.5 mL solution for injection
Ovaleap 450 IU/0.75 mL solution for injection
Ovaleap 900 IU/1.5 mL solution for injection

follitropin alfa

Read all of this leaflet carefully before you start using 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, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Ovaleap is and what it is used for
2. What you need to know before you use Ovaleap
3. How to use Ovaleap
4. Possible side effects
5. How to store Ovaleap
6. Contents of the pack and other information

1. What Ovaleap is and what it is used for

What Ovaleap is

This medicine contains the active substance follitropin alfa, which is almost identical to a natural hormone produced by your body called “follicle-stimulating hormone” (FSH). FSH is a gonadotropin, a type of hormone that plays an important role in human fertility and reproduction. In women, FSH is needed for the growth and development of the sacs (follicles) in the ovaries that contain the egg cells. In men, FSH is needed for the production of sperm.

What Ovaleap is used for

In adult women, Ovaleap is used:

- to help ovulation (release of a mature egg cell from the follicle) in women that cannot ovulate and that have not responded to treatment with a medicine called “clomifene citrate”.
- to help follicles develop in women undergoing assisted reproductive technology procedures (procedures that may help you to become pregnant) such as “*in vitro* fertilisation”, “gamete intra-fallopian transfer” or “zygote intra-fallopian transfer”.
- in combination with a medicine called “lutropin alfa” (a version of another gonadotropin, “luteinising hormone” or LH) to help ovulation in women whose body is producing too little FSH and LH.

In adult men, Ovaleap is used:

- in combination with a medicine called “human chorionic gonadotropin” (hCG) to help produce sperm in men that are infertile due to low levels of certain hormones.

2. What you need to know before you use Ovaleap

Do not use Ovaleap:

- if you are allergic to follitropin alfa, follicle stimulating hormone (FSH) or any of the other ingredients of this medicine (listed in section 6).
- if you have a tumour in your hypothalamus or pituitary gland (parts of the brain).
- if you are a **woman** with:
 - large ovaries or sacs of fluids within the ovaries (ovarian cysts) of unknown origin.
 - unexplained vaginal bleeding.
 - cancer in your ovaries, womb or breasts.
 - any condition that usually makes normal pregnancy impossible, such as ovarian failure (early menopause), fibroid tumours of the womb or malformed reproductive organs.
- if you are a **man** with:
 - testicular failure that is not treatable.

Do not use this medicine if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before using this medicine.

Warnings and precautions

Before the treatment is started you and your partner's fertility should be evaluated by a doctor experienced in treating fertility disorders.

Talk to your doctor, pharmacist or nurse before using Ovaleap.

Porphyria

Tell your doctor before you start treatment, if you or any member of your family have porphyria. This is a condition that may be passed on from parents to children which means that you have an inability to break down porphyrins (organic compounds).

Tell your doctor straight away if:

- your skin becomes fragile and easily blistered, especially skin that has been frequently in the sun, and/or
- you have stomach, arm or leg pain.

If you experience the above symptoms your doctor may recommend that you stop treatment.

Ovarian hyper-stimulation syndrome (OHSS)

If you are a woman, this medicine increases your risk of developing OHSS. This is when your follicles develop too much and become large cysts.

Talk to your doctor straight away if:

- you get pain in the lower part of the abdomen (belly),
- you gain any weight rapidly,
- you feel sick or are vomiting,
- you have difficulty in breathing.

If you experience the above symptoms your doctor might ask you to stop using this medicine (see also section 4 under "Serious side effects in women").

If you are not ovulating and if the recommended dose and timing are followed, the occurrence of OHSS is less likely. Ovaleap treatment seldom causes severe OHSS unless the medicine that is used for final follicular maturation (containing human chorionic gonadotropin, hCG) is given. If you are developing OHSS your doctor may not give you any hCG in this treatment cycle. You may be told not to have sex or to use a barrier contraceptive method for at least 4 days.

Multiple pregnancy

When using this medicine, you have a higher risk of being pregnant with more than one child (i.e. "multiple pregnancy", typically twins) than if you conceived naturally. Multiple pregnancy may lead to medical complications for you and your babies. You can reduce the risk of multiple pregnancy by using the right dose of this medicine at the right times. When undergoing assisted reproductive

technology the risk of having a multiple pregnancy is related to your age, the quality and number of fertilised eggs or embryos placed inside you.

Miscarriage

You are more likely to have a miscarriage than the average woman when undergoing assisted reproductive technology or stimulation of your ovaries to produce eggs.

Ectopic pregnancy

You are more likely to have a pregnancy outside the womb (an ectopic pregnancy) than the average woman when undergoing assisted reproductive technology and if you have damaged fallopian tubes.

Birth defects

When being conceived by assisted reproductive technology, a baby may have a slightly higher risk of birth defects than after natural conception. This could be related to multiple pregnancies or to parent characteristics such as maternal age and sperm characteristics.

Blood clotting problems (thromboembolic events)

If you have ever had blood clots in your leg or lung, or a heart attack or stroke, or if your family have experienced these, inform your doctor. You might have a higher risk of these problems occurring or becoming worse with Ovaleap treatment.

Men with too much FSH in their blood

If you are a man, having too much natural FSH in your blood can be a sign of damaged testicles. This medicine usually does not work if you have this problem. If your doctor decides to try Ovaleap treatment, they may monitor it by asking you to provide semen for analysis 4 to 6 months after starting treatment.

Children and adolescents

This medicine is not for use in children and adolescents below 18 years of age.

Other medicines and Ovaleap

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

- If you use Ovaleap with other medicines which help ovulation such as human chorionic gonadotropin (hCG) or clomifene citrate, this may increase the response of your follicles.
- If you use Ovaleap at the same time as a “gonadotropin-releasing hormone” (GnRH) agonist or antagonist (these medicines reduce your sex hormone levels and stop you ovulating) you may need a higher dose of Ovaleap to produce follicles.

Pregnancy and breast-feeding

You should not use this medicine if you are pregnant or breast-feeding.

Driving and using machines

This medicine does not affect your ability to drive and use machines.

Ovaleap contains sodium, benzalkonium chloride and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose that is to say essentially ‘sodium-free’.

This medicine also contains 0.02 mg per mL of benzalkonium chloride and 10.0 mg per mL of benzyl alcohol. Ask your doctor or pharmacist for advice if you have a liver or kidney disease, and if you are pregnant or breast-feeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).

3. How to use Ovaleap

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

This medicine is given as an injection into the tissue just under the skin (subcutaneous injection). Your doctor or nurse will show you how to inject the medicine. If you administer this medicine to yourself, please carefully read and follow the “Instructions for Use” of the pen.

What the recommended dose is

Your doctor will decide how much medicine you will take and how often. The doses described below are stated in International Units (IU).

Women

If you are not ovulating and have irregular or no periods

- This medicine is usually given every day.
- If you have irregular periods, start using this medicine within the first 7 days of your menstrual cycle. If you do not have periods, you can start using the medicine on any convenient day.
- The usual starting dose of this medicine is 75 to 150 IU each day.
- Your dose of this medicine may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.
- The maximum daily dose of this medicine is usually not higher than 225 IU.
- When you get the desired response, you will be given hCG or “recombinant hCG” (r-hCG, an hCG made in a laboratory by a special DNA technique). The single injection will be 250 micrograms of r-hCG or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last Ovaleap injection. The best time to have sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination may be performed by placing the sperm into the womb cavity.

If your doctor cannot see a desired response after 4 weeks, that treatment cycle with Ovaleap should be stopped. For the following treatment cycle, your doctor will give you a higher starting dose of this medicine than before.

If your body responds too strongly, your treatment will be stopped and you will not be given any hCG [see also section 2 under “Ovarian hyper-stimulation syndrome (OHSS)”]. For the following cycle, your doctor will give you a lower dose of Ovaleap than before.

If you need to develop several eggs for collection prior to any assisted reproductive technology

- The usual starting dose of this medicine is 150 to 225 IU each day, from day 2 or 3 of your menstrual cycle.
- The dose may be increased, depending on your response. The maximum daily dose is 450 IU.
- Treatment is continued until your eggs have developed to a desired point. This usually takes about 10 days but can take any time between 5 and 20 days. Your doctor will use blood tests and/or an ultrasound machine to check when this is.
- When your eggs are ready, you will be given hCG or r-hCG. The single injection will be 250 micrograms of r-hCG or 5 000 to 10 000 IU of hCG, 24 to 48 hours after the last Ovaleap injection. This gets your eggs ready for collection.

In other cases, your doctor may first stop you from ovulating by using a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Then Ovaleap is given approximately 2 weeks after the start of agonist treatment. The Ovaleap and GnRH agonist are then both given until your follicles develop as desired.

If you have been diagnosed with very low levels of FSH and LH hormones

- The usual starting dose of Ovaleap is 75 to 150 IU together with 75 IU of lutropin alfa.
- You will use these two medicines each day for up to 5 weeks.
- Your dose of Ovaleap may be increased every 7 or every 14 days by 37.5 to 75 IU, until you get the desired response.

- When you get the desired response, you will be given hCG or r-hCG. The single injection will be 250 micrograms of r-hCG or 5 000 to 10 000 IU of hCG, 24 to 48 hours after your last injections of Ovaleap and lutropin alfa. The best time to have sex is on the day of the hCG injection and the day after. Alternatively, intrauterine insemination or another medically assisted reproduction procedure may be performed based on your doctor's judgment.

If your doctor cannot see a response after 5 weeks, that treatment cycle should be stopped. For the following cycle, your doctor will give you a higher starting dose of this medicine than before.

If your body responds too strongly, your treatment with Ovaleap will be stopped and you will not be given any hCG [see also section 2 under "Ovarian hyper-stimulation syndrome (OHSS)"]. For the following cycle, your doctor will give you a lower dose of Ovaleap than before.

Men

- The usual dose of this medicine is 150 IU together with hCG.
- You will use these two medicines three times a week for at least 4 months.
- If you have not responded to treatment after 4 months, your doctor may suggest that you continue using these two medicines for at least 18 months.

How are the injections given?

This medicine is given as an injection into the tissue just under the skin (subcutaneous injection) using the Ovaleap Pen. The Ovaleap Pen is a device (a "pen") used for giving injections into the tissue just under the skin.

Your doctor may suggest that you learn how to inject yourself with this medicine. Your doctor or nurse will give you instructions on how to do this and you can also find instructions in the separate instructions for use of the pen. Do not attempt to self-administer this medicine without this training by your doctor or nurse. The very first injection of this medicine should only be given in the presence of a doctor or nurse.

Ovaleap solution for injection in cartridges has been developed for use in the Ovaleap Pen. You must follow the separate instructions for use of the Ovaleap Pen carefully. The instructions for use of the pen will be provided together with the Ovaleap Pen. Proper treatment of your condition, however, requires close and constant co-operation with your doctor.

Discard used needles immediately after injection.

If you use more Ovaleap than you should

The effects of using too much Ovaleap are unknown. Nevertheless one could expect ovarian hyper-stimulation syndrome (OHSS) to occur, which is described in section 4 under "Serious side effects in women". However, the OHSS will only occur if hCG is also administered [see also section 2 under "Ovarian hyper-stimulation syndrome (OHSS)"].

If you forget to use Ovaleap

Do not use a double dose to make up for a forgotten dose. Please talk to your doctor as soon as you realise that you forgot a dose.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Important side effects

Serious side effects in men and women

- Allergic reactions such as skin rash, raised itchy areas of skin and severe allergic reactions with weakness, drop in blood pressure, difficulty breathing and swelling of the face have been reported very rarely (may affect up to 1 in 10 000 people). If you think you are having this type of reaction, you must stop your Ovaleap injection and get medical help immediately.

Serious side effects in women

- Lower stomach ache together with nausea or vomiting may be the symptoms of ovarian hyper-stimulation syndrome (OHSS). This may indicate that the ovaries over-reacted to the treatment and that large ovarian cysts developed [see also section 2 under “Ovarian hyper-stimulation syndrome (OHSS)”]. This side effect is common (may affect up to 1 in 10 people).
- OHSS may become severe with clearly enlarged ovaries, decreased urine production, weight gain, difficulty in breathing and/or possible fluid accumulation in your stomach or chest. This side effect is uncommon (may affect up to 1 in 100 people).
- Complications of OHSS such as twisting of ovaries or blood clotting may occur rarely (may affect up to 1 in 1 000 people).
- Serious blood clotting complications (thromboembolic events), sometimes independent of OHSS, may be found very rarely (may affect up to 1 in 10 000 people). This could cause chest pain, breathlessness, stroke or heart attack [see also section 2 under “Blood clotting problems (thromboembolic events)”].

If you notice any of the above-listed side effects you should immediately contact your doctor who may ask you to stop using Ovaleap.

Other side effects in women

Very common (may affect more than 1 in 10 people)

- Local reactions at the injection site, such as pain, redness, bruising, swelling and/or irritation
- Headache
- Sacs of fluid within the ovaries (ovarian cysts)

Common (may affect up to 1 in 10 people)

- Stomach ache
- Abdominal bloating
- Abdominal cramps
- Feeling sick
- Vomiting
- Diarrhoea

Very rare (may affect up to 1 in 10 000 people)

- Your asthma may get worse.

Other side effects in men

Very common (may affect more than 1 in 10 people)

- Local reactions at the injection site, such as pain, redness, bruising, swelling and/or irritation

Common (may affect up to 1 in 10 people)

- Swelling of the veins above and behind the testicles (a varicocele)
- Breast development
- Acne
- Weight gain

Very rare (may affect up to 1 in 10 000 people)

- Your asthma may get worse.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ovaleap

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 label and outer carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C - 8 °C).

Do not freeze.

Keep the cartridge in the outer carton in order to protect from light.

Before opening and within its shelf life, you may remove this medicine from the refrigerator, without being refrigerated again, for up to 3 months. Do not store above 25 °C. You must discard this medicine if it has not been used after 3 months.

Once opened, the cartridge in-use in the pen may be stored for a maximum of 28 days. Do not store above 25 °C. Write down the date of first use in the patient diary, which will be provided with the Ovaleap Pen.

Put the pen cap back on the Ovaleap Pen after each injection in order to protect the cartridge from light.

Do not use this medicine if you notice it is cloudy or there are particles in it.

Do not throw away any medicines via wastewater. 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 Ovaleap contains

- The active substance is follitropin alfa.
Ovaleap 300 IU/0.5 mL: Each cartridge contains 300 IU (equivalent to 22 micrograms) follitropin alfa in 0.5 mL solution.
Ovaleap 450 IU/0.75 mL: Each cartridge contains 450 IU (equivalent to 33 micrograms) follitropin alfa in 0.75 mL solution.
Ovaleap 900 IU/1.5 mL: Each cartridge contains 900 IU (equivalent to 66 micrograms) follitropin alfa in 1.5 mL solution.
Each mL of the solution contains 600 IU (equivalent to 44 micrograms) follitropin alfa.
- The other ingredients are sodium dihydrogen phosphate dihydrate, sodium hydroxide (2 M) (for pH adjustment), mannitol, methionine, polysorbate 20, benzyl alcohol, benzalkonium chloride and water for injections.
All strengths listed above contain the other ingredients.

What Ovaleap looks like and contents of the pack

Ovaleap is a solution for injection (injection). Ovaleap is a clear and colourless solution.

Ovaleap 300 IU/0.5 mL is available in packs containing 1 cartridge and 10 injection needles.
Ovaleap 450 IU/0.75 mL is available in packs containing 1 cartridge and 10 injection needles.
Ovaleap 900 IU/1.5 mL is available in packs containing 1 cartridge and 20 injection needles.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Theramex Ireland Limited
3rd Floor, Kilmore House
Park Lane, Spencer Dock
Dublin 1
D01 YE64
Ireland

Manufacturer

Merckle GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

Rechon Life Science AB
Soldattorpsvägen 5
216 13 Limhamn
Sweden

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