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

This medicine can be sold under doctor's prescription only

PUREGON® SOLUTION FOR INJECTION 150 IU, 300 IU, 600 IU, 900 IU

Solution for Injection

Each cartridge contains:
Follitropin beta 150 IU/ 0.18 ml
Follitropin beta 300 IU/ 0.36 ml
Follitropin beta 600 IU/ 0.72 ml
Follitropin beta 900 IU/ 1.08 ml

For a list of inactive ingredients see section 6.1 "**What PUREGON contains**".

Read all of this leaflet carefully before you start using this medicine.

- This leaflet contains concise information about **PUREGON**. 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 medical condition seems similar to yours.
- **PUREGON** is not intended for use in children.
- **PUREGON** is not intended for pregnant women.

1. WHAT IS THE MEDICINE INTENDED FOR?

PUREGON is used to treat infertility in any of the following situations:

Women

In women who do not ovulate and do not respond to treatment with clomifene citrate, **PUREGON** can be used to cause ovulation.

In women undergoing assisted reproduction techniques, including in vitro fertilisation (IVF) and other methods, **PUREGON** can bring about the development of multiple follicles.

Men

In men who are infertile due to lowered hormone levels, **PUREGON** can be used for the production of sperm.

Therapeutic group: Gonadotrophins (sex hormones).

PUREGON solution for injection contains follitropin beta, a hormone known as follicle-stimulating hormone (FSH).

FSH belongs to the group of gonadotrophins (sex hormones), which play an important role in human fertility and reproduction. In women, FSH is needed for the growth and development of follicles in the ovaries. Follicles are small round sacs that contain the egg cells.

In men, FSH is needed for the production of sperm.

2. BEFORE YOU TAKE PUREGON

2.1 Do not use PUREGON if you:

- are hypersensitive (allergic) to follitropin beta or any of the other ingredients of **PUREGON** (listed in section 6.1)
- have a tumour of the ovary, breast, uterus, testis or brain (pituitary gland or hypothalamus)
- have heavy or irregular vaginal bleeding where the cause is unknown.
- have ovaries that do not work because of a condition called primary ovarian failure
- have ovarian cysts or enlarged ovaries not caused by polycystic ovarian syndrome (PCOS)
- have malformations of the sexual organs which make a normal pregnancy impossible

- have fibroid tumours in the uterus which make a normal pregnancy impossible
- are a man and are infertile because of a condition called primary testicular failure.

2.2 Special warnings concerning use of PUREGON

Before starting treatment with PUREGON, tell your doctor if you:

- have had an allergic reaction to certain antibiotics (neomycin and/or streptomycin)
- have uncontrolled pituitary gland or hypothalamic problems
- have an underactive thyroid gland (hypothyroidism)
- have adrenal glands that are not working properly (adrenocortical insufficiency)
- have high prolactin levels in the blood (hyperprolactinemia)
- have any other medical conditions (for example, diabetes, heart disease, or any other long-term disease).

If you are a woman:

Ovarian hyperstimulation syndrome (OHSS)

Your doctor will check the effects of the treatment regularly to be able to choose the correct dose of **PUREGON** from day to day. You may regularly have ultrasound scans of the ovaries. Your doctor may also check blood hormone levels. This is very important since too high a dose of FSH may lead to rare but serious complications in which the ovaries are overly stimulated and the growing follicles become larger than normal. This serious medical condition is called ovarian hyperstimulation syndrome (OHSS). In rare cases, severe OHSS may be life-threatening. OHSS causes fluid to build up suddenly in your stomach and chest areas and can cause blood clots to form. Call your doctor right away if you notice severe abdominal swelling, pain in the stomach area (abdomen), feeling sick (nausea), vomiting, sudden weight gain due to fluid buildup, diarrhoea, decreased urine output or trouble breathing (see also section 4, "**SIDE EFFECTS**").
→ Regular monitoring of the response to FSH-treatment helps to prevent ovarian overstimulation.
Contact your doctor immediately if you are experiencing stomach pains, also if this occurs some days after the last injection has been given.

Multiple Pregnancy or birth defects

After treatment with gonadotrophin preparations, there is an increased chance of having multiple pregnancies, even when only one embryo is transferred into the uterus. Multiple pregnancies carry an increased health risk for both the mother and her babies around the time of birth. Furthermore, multiple pregnancies and characteristics of the patients undergoing fertility treatment (e.g. age of the female, sperm characteristics, genetic background of both parents) may be associated with an increased risk of birth defects.

Pregnancy complications

There is a slightly increased risk of a pregnancy outside the uterus (an ectopic pregnancy). Therefore, your doctor should perform an early ultrasound examination to exclude the possibility of pregnancy outside the uterus.
In women undergoing fertility treatment there may be a slightly higher chance of a miscarriage.

Blood clot (Thrombosis)

Treatment with **PUREGON**, just as pregnancy itself, may increase the risk of having a blood clot (thrombosis). Thrombosis is the formation of a blood clot in a blood vessel.
Blood clots can lead to serious medical conditions, such as:

- blockage in your lungs (pulmonary embolus)
- stroke
- heart attack
- blood vessel problems (thrombophlebitis)
- a lack of blood flow (deep venous thrombosis) that may result in a loss of your arm or leg.

Please discuss this with your doctor, before starting treatment, especially:

- if you already know you have an increased chance of having thrombosis

- if you, or anyone in your immediate family, have ever had a thrombosis
- if you are severely overweight.

Ovarian torsion
Ovarian torsion has been reported and may occur after treatment with gonadotropins including **PUREGON**. Ovarian torsion is the twisting of an ovary. Twisting of the ovary could cause the blood flow to the ovary to be cut off.
Before starting to use this medicine, tell your doctor if you:
- have ever had ovarian hyperstimulation syndrome OHSS
- are pregnant or think that you may be pregnant
- have ever had stomach (abdominal) surgery
- have ever had a twisting of an ovary
- have past or current cysts in your ovary or ovaries.

Ovarian and Other Reproductive System Tumours
There have been reports of ovarian and other reproductive system tumors in women who have had infertility treatment. It is not known if treatment with fertility medicines increases the risk of these tumors in infertile women.

Other medical conditions
In addition, before starting to use this medicine, tell your doctor if you:
- have been told by a doctor that pregnancy would be dangerous for you.

If you are a man:

Men with too much FSH in their blood
Increased FSH blood levels are a sign of damage to the testicles. **PUREGON** is usually not effective in such cases. To check the effects of treatment, your doctor may ask you for a semen sample to be analysed, four to six months after the start of treatment.

2.3 Taking other medicines
If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, you should tell the attending doctor or pharmacist.
If **PUREGON** is used in a combination with clomifene citrate, the effect of **PUREGON** may be increased. If a GnRH agonist (a medicine used to prevent early ovulation) has been given, higher doses of **PUREGON** may be needed.

2.4 Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. You should not use **PUREGON** if you are already pregnant, or think you might be pregnant.
PUREGON may affect milk production. It is unlikely that **PUREGON** is passed into breast milk. If you are breast-feeding, tell your doctor before using **PUREGON**.

2.5 Driving and using machines
PUREGON is unlikely to affect your ability to drive or use machines.

2.6 Important information about some of the ingredients of PUREGON
This medicinal product contains less than 1 mmol sodium (23 mg) per injection, i.e. essentially “sodium-free”.

2.7 Children
PUREGON is not intended for use in children.

3. HOW TO TAKE PUREGON?

Always take **PUREGON** as instructed by the doctor. You should check with your doctor or pharmacist if you are not sure.
The dosage and duration of treatment will be determined by the doctor only.
The usually recommended dose is:

Dosage in women

Your doctor will decide on your starting dose. This dose may be adjusted during your treatment period. Further details on the treatment schedule are given below.
There are large differences between women in the response of the ovaries to FSH, which makes it impossible to set a dosage schedule which is suitable for all patients. To find the right dosage, your doctor will check your follicle growth by means of ultrasound scanning, and measurement of the amount of oestradiol (female sex hormone) in the blood.

* *Women who are not ovulating*
  A starting dose is set by your doctor. This dose is continued for at least seven days. If there is no ovarian response, the daily dose will then be gradually increased until follicle growth and/or plasma oestradiol levels indicate a proper response. The daily dose is then maintained until a follicle of proper size is present. Usually, 7 to 14 days of treatment are sufficient. **PUREGON** treatment is then stopped and ovulation will be induced by giving human chorionic gonadotrophin (hCG).
* *Medically assisted reproduction programs, for instance IVF*
  A starting dose is set by your doctor. This dose is continued for at least the first four days. After this, your dose may be adjusted, based upon your ovarian response. When a sufficient number of follicles of proper size are present, the final phase of maturation of the follicles is induced by giving hCG. Retrieval of the egg(s) is performed 34-35 hours later.

Dosage in men

PUREGON is usually prescribed at a dose of 450 IU per week, mostly in 3 dosages of 150 IU, in combination with another hormone (hCG), for at least 3 to 4 months. The treatment period equals the development time of sperm and the time in which improvement can be expected. If your sperm production has not started after this period, your treatment may carry on for at least 18 months.

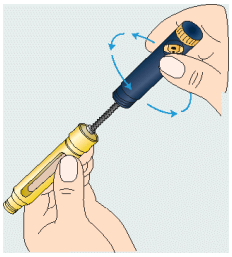
Do not exceed the recommended dose.

How are the injections given

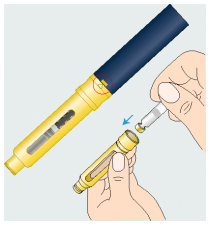
The very first injection of **PUREGON** should only be given in the presence of a doctor or nurse.
PUREGON solution for injection in cartridges has been developed for use in the Puregon Pen. The separate instructions for using the pen must be followed carefully. Do not use the cartridge if the solution contains particles or if the solution is not clear.
Using the pen, injections just under the skin (in the lower stomach, for example) can be given by yourself or your partner. Your doctor will tell you when and how to do this. If you inject yourself with **PUREGON**, follow the instructions carefully to give **PUREGON** properly and with minimal discomfort.

Instructions for injection

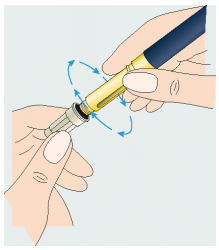
1. Take the pen out of its case, remove the cap from the pen, unscrew the body from the cartridge holder.



2. Insert the **PUREGON** cartridge into the cartridge holder with the cap of the cartridge going in first. Screw the pen on again. Make sure that no gap is left and that the blue arrow marked at the end of the cartridge holder points to the yellow mark at the end of the pen body.

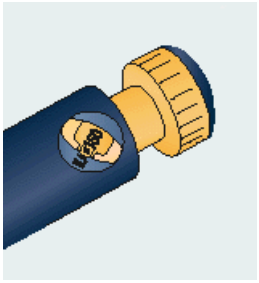


3. Use a new needle for each injection. Before attaching the needle, disinfect the end of the **PUREGON** cartridge (placed inside the pen) and the open end of the cartridge holder with some alcohol.
Remove the paper seal from the outer needle shield and push the pen steadily into the needle shield. Screw the needle in firmly. Remove the outer and inner needle shield.

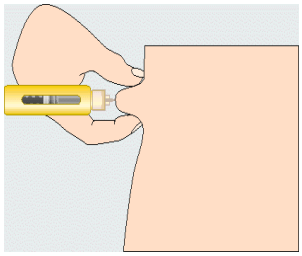


4. Hold the pen with the needle pointing upwards, gently tap the cartridge holder with your finger to allow the air bubbles to rise to the top of the needle. A droplet of liquid will form at the tip of the needle.
If you do not see liquid at the tip of the needle, dial the dosage knob one click and press the injection button. Make sure that a droplet of liquid has formed at the tip of the needle. Repeat this step until a droplet is observed at the tip of the needle.
The pen is now ready for injecting **PUREGON**.

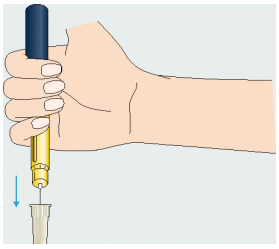
5. Dial the orange dosage knob until the dot located between the two marks in the middle of the dosage scale is aligned with the desired dose prescribed by your doctor.
If you accidentally dialed past the correct dose, turn the dosage knob past the 450 IU mark, as far as it will turn. The dosage scale should move freely.
Press the injection button in and begin to readjust the dosage, from zero upwards. No medicine is lost in this process.
If you try to correct your error by dialing in the opposite direction you will get the exact dose, but will lose some of the medicine.

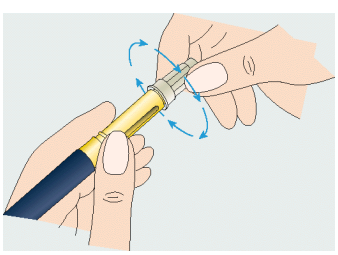


6. Disinfect the injection site with alcohol, and let the alcohol dry somewhat before continuing.
It is advisable to administer the injection in the abdomen, below the navel.
Pinch the skin where you will administer the injection between your thumb and forefinger and with your other hand insert the entire needle into the skin at a 90 degree angle.
Press the injection button and inject until the dosage scale shows “0”.
Wait 5 seconds before removing the needle from the skin. Pull the needle out gently and place a sterile pad on the injection site.



7. Insert the needle into the outer needle shield. Remove the needle from the pen and store the pen in a safe place.





If you use more PUREGON than you should
Tell your doctor immediately.

Too high a dose of **PUREGON** may cause hyperstimulation of the ovaries (OHSS). This may be noticed as pain in the stomach. If you are troubled by stomach pains, tell your doctor immediately (see also section 4, "**SIDE EFFECTS**").
If you have taken an overdose, or if a child has accidentally swallowed the medicine, proceed immediately to a hospital emergency room and bring the package of the medicine with you.

If you forget to use PUREGON
If you forget a dose do not use a double dose to make up for a missed dose.
→ Contact your doctor.
How can you contribute to the success of the treatment?
Do not take medicines in the dark! Check the label and the dose each time you take your medicine. Wear glasses if you need them.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. SIDE EFFECTS
Like all medicines, **PUREGON** can cause side effects, in some of the users.
Do not be alarmed by reading the list of side effects, you may not suffer from any of them.

Serious side effects in women
A complication with FSH treatment is hyperstimulation of the ovaries. Ovarian overstimulation may develop into a medical condition called **ovarian hyperstimulation syndrome (OHSS)**, which can be a serious medical problem. The risk can be reduced by careful monitoring of follicular development during treatment. Your doctor will do ultrasound scans of your ovaries to carefully monitor the number of maturing follicles. Your doctor may also check blood hormone levels. Pain in the stomach, feeling sick or diarrhoea are the first symptoms. In more severe cases symptoms may include enlargement of the ovaries, accumulation of fluid in the abdomen and/or chest (which may cause sudden weight gain due to fluid buildup) and the occurrence of blood clots in the circulation (see section 2.2, "**Special warnings concerning use of PUREGON**").
→ Contact your doctor immediately if you are experiencing stomach pains, or any of the other symptoms of ovarian hyperstimulation, also if this occurs some days after the last injection.

If you are a woman:
Common side effects (may affect up to 1 in 10 people):
- Headache
- Injection site reactions (such as bruising, pain, redness, swelling and itching)
- Ovarian hyperstimulation syndrome (OHSS)
- Pelvic pain
- Stomach pain and/or bloating

Uncommon side effects (may affect up to 1 in 100 people):
- Breast complaints (including tenderness)
- Diarrhoea, constipation or stomach discomfort
- Enlargement of the uterus
- Feeling sick (nausea)
- Hypersensitivity reactions (such as rash, redness, hives and itching)
- Ovarian cysts or enlargement of the ovaries
- Ovarian torsion (twisting of the ovaries)
- Vaginal bleeding

Rare side effects (may affect up to 1 in 1,000 people):
- Blood clots (this may also occur in the absence of unwanted overstimulation of the ovaries, see section 2.2, "**Special warnings concerning use of PUREGON**").

Pregnancy outside the uterus (an ectopic pregnancy), miscarriage and multiple pregnancies have also been reported. These side effects are not considered to be related to the use of **PUREGON**, but to Assisted Reproductive Technology (ART) or subsequent pregnancy.

If you are a man:
Common side effects (may affect up to 1 in 10 people):
- Acne
- Injection site reactions (such as hardening and pain)
- Headache
- Rash
- Some breast development
- Testicular cyst

If a side effect appears, if any of the side effects gets serious or if you notice a side effect not mentioned in this leaflet, consult your doctor.

Side effects can be reported to the Ministry of Health by using the online form for adverse events reporting which is on the Ministry of Health Homepage: www.health.gov.il

or by following the link:
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic%40moh.health.gov.il

5. HOW TO STORE PUREGON?

- Avoid Poisoning! This medicine, as all other medicines, must be stored 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 a doctor!
- Do not use **PUREGON** after the expiry date (exp. date) which is stated on the pack. The expiry date refers to the last day of the indicated month.

Storage conditions:
Store in a refrigerator (2°C – 8°C). Do not freeze.
May be stored by the patient at or below 25ºC for a single period of not more than three months.
Keep the medicine in the outer carton.
Make a note of when you start storing the product out of the refrigerator.
Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days.
Please put the day of first use of the cartridge on the dosing record table as shown in the Instruction Manual of the Puregon Pen.
Discard used needles immediately after injection.
Do not mix any other drug into the cartridges. Empty cartridges must not be refilled.

- Medicines should not be disposed of 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

6.1 What PUREGON contains?

- The active substance is: follitropin beta.
- **PUREGON** cartridge contains either: 150 IU, 300 IU, 600 IU, 900 IU of follitropin beta.
- In addition to the active ingredient the medicine also contains inactive ingredients: sucrose, sodium citrate, L-methionine, polysorbate 20 and benzyl alcohol in water for injections. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

6.2 What PUREGON looks like and contents of the pack

PUREGON solution for injection is a clear, colourless aqueous solution.
Pack size:

PUREGON 300 IU is available in packs of 1 multi-dose cartridge of 0.480 ml, and 2 packs with 3 pen needles each.
PUREGON 600 IU is available in packs of 1 multi-dose cartridge of 0.840 ml, and 2 packs with 3 pen needles each.
PUREGON 900 IU is available in packs of 1 multi-dose cartridge of 1.230 ml, and 3 packs with 3 pen needles each.

Marketing authorization holder:
Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O.Box 7121, Petah-Tikva 49170.

Manufacturer:
Merck Sharp & Dohme Corp., New-Jersey, USA.

This Leaflet was checked and approved by the Ministry of Health on October 2015

Drug registration no. listed in the official registry of the Ministry of Health:
PUREGON solution for injection: 130.52.30898