

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PUREGON® (follitropin beta)

This leaflet is part III of a three-part “Product Monograph” published when PUREGON® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PUREGON®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

The name of your medicine is PUREGON®. It contains follicle-stimulating hormone (FSH) in a solution in a cartridge, corresponding to 300, 600 or 900 international units (IU) net total dose per cartridge or solution for injection 100 international units (IU) per vial. PUREGON® is produced by mammalian cells, which by recombinant DNA technology were changed to carry the genes for human FSH.

PUREGON® belongs to a group of medicines called “gonadotropins”.

What it does:

PUREGON® is very similar to the natural human FSH, which is normally secreted by a small gland at the base of the brain, the pituitary. Together with luteinizing hormone (LH), FSH controls the action of the sexual glands (ovaries in women and testes in men).

In women FSH is important for the monthly ripening of the follicle, a tiny cyst in the ovary in which the egg cell develops. If the body does not produce enough FSH, infertility may be the result. In these cases PUREGON® can be used to make up for the shortage. To determine the right dosage, a daily check may be necessary. Follicle ripening is determined by means of ultrasound, and the amount of estrogens (female hormones) in blood can be measured. When the follicle is big enough, a hormone preparation with a strong LH activity is given (human chorionic gonadotropin, hCG). This causes ovulation (release of the egg).

In spite of careful monitoring, often more than one egg cell is released. This increases the chance of

having more than one baby.

Poor production of FSH is not the only reason for infertility. In these cases medically assisted reproduction programs can sometimes be used, for instance *in vitro* (“test tube”) fertilization. For this technique several egg cells are needed and PUREGON® can then be used to cause a number of egg cells to develop.

In men, it is used to increase the production of sperm in those who have a deficiency due to hypogonadotropic hypogonadism.

When it should not be used:

Do not use PUREGON® if you are hypersensitive to follitropin beta or any of the other ingredients of PUREGON®, or if you have a tumour of the ovaries, breasts, uterus, testis, pituitary gland, or if you suffer from primary testicular failure.

Treatment with gonadotropins may increase the risk of having a blood clot (thrombosis). Thrombosis is the formation of a blood clot in your veins or arteries. Please tell your doctor prior to starting treatment, if you already know you have an increased risk for thrombosis, if you or anyone in your immediate family has ever had a thrombosis, or if you are severely overweight. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.

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.

Close supervision of patients by a doctor is very important. Usually ultrasound scans of the ovaries are performed. Your doctor may also check blood hormone levels. The results of these tests allow the doctor to choose the proper dose from day to day. This is very important since too high a dose 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, diarrhea, decreased

urine output or trouble breathing.

Ovarian Torsion: Ovarian torsion has occurred 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.

If you are a man: Elevated FSH blood levels are indicative of testicular damage. PUREGON® is usually not effective in such cases. To monitor treatment, your doctor may ask for a semen analysis to be performed 4 to 6 months after the beginning of treatment.

Pregnancy: In pregnancies occurring after treatment with gonadotropic preparations, there is an increased risk of having twins or multiple births.

There is a slightly increased risk of a pregnancy outside of the uterus (an ectopic pregnancy). Early ultrasound confirmation that a pregnancy is intra-uterine is therefore important.

Ability to drive or operate machinery: As far as is known, PUREGON® has no effect on alertness and concentration.

What the medicinal ingredient is:

Follitropin beta

What the important nonmedicinal ingredients are:

In addition to FSH, both the solution in cartridges and the solution for injection contain L-methionine, polysorbate 20, sucrose, sodium citrate, and water for injection. Additionally, the solution in cartridges contains benzyl alcohol.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

PUREGON® only works if it is injected. It is presented as a sterile solution in cartridges in strength of 833 IU/mL. The 300 IU/0.36 mL cartridge contains 0.480 mL for a net total deliverable dose of 300 IU, the 600 IU/0.72 mL cartridge contains 0.840 mL for a net total deliverable dose of 600 IU and the 900 IU/1.08 mL cartridge contains 1.23 mL for a net total deliverable dose of 900 IU.

The net total dose per 300, 600 or 900 IU cartridge is based on a maximum number of 6, 6 or 9 injections, respectively. When more injections are given the net total may be lowered, because each injection has to be preceded by an air shot. Air shots are used to remove excess air from the cartridge and the needle. (For example, for the 300 IU cartridge when administering a 50 IU dose, a maximum of 6

injections can be delivered for a net dose of 300 IU respectively. For the 600 & 900 IU cartridge, when administering a 100 IU dose, a maximum of 6 & 9 injections can be delivered for a net dose of 600 & 900 IU respectively).

PUREGON® is also presented as a sterile solution for injection. The 100 IU/0.5 mL vial containing the sterile solution has a red coloured tamper-evident disc, which is flipped off prior to insertion of the syringe needle.

WARNINGS AND PRECAUTIONS

BEFORE you use PUREGON® talk to your doctor or pharmacist:

- **Current conditions do not use this medication if you have;**
 - A high circulating FSH level indicating primary ovarian failure or primary testicular failure
 - Uncontrolled thyroid or adrenal dysfunction
 - Tumour of the ovary, breast, uterus, testis or brain (hypothalamus or pituitary gland)
 - Pregnancy, suspected pregnancy or lactation
 - Heavy or irregular vaginal bleeding of undetermined origin
 - Ovarian cyst or enlargement not due to polycystic syndrome (PCOS)
 - Are allergic (hypersensitive) to follitropin beta or any of the other ingredients of PUREGON®
 - Conditions incompatible with pregnancy such as malformations of reproductive organs or fibroid tumours of the uterus

- **Before starting to use this medicine, it is important to inform your doctor if you:**
 - Have experienced an allergic reaction to neomycin and/or streptomycin (antibiotics) in the past.
 - 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:
 - 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.
- **Past diseases**
 - Women with risk factors for thrombosis (previous episode of thrombosis, family history of thrombosis or a genetic condition that predisposes her to thrombosis) may have an increased risk of a venous or arterial thromboembolic event upon treatment with gonadotropins.
 - **Reproductive issues**
 - After treatment with gonadotropin 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. There are also potential risks associated with multiple births including a higher rate of spontaneous abortion.
 - There is a slightly increased risk of a pregnancy outside of the uterus (an ectopic pregnancy). Therefore, your doctor should perform an early ultrasound examination to exclude the possibility of pregnancy outside the uterus.
 - There have been reports of ovarian and other reproductive system tumours in women who have had infertility treatment. It is not known if treatment with fertility medicines increases the risk of these tumours 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.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with PUREGON[®] include: clomiphene

PROPER USE OF THIS MEDICATION

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.

Usual Dose:

Dosage in the female:

Your doctor will decide on the dose of PUREGON[®] to be given. This dose may be increased as your treatment progresses.

There are large differences between women in the response of the ovaries to FSH which makes it impossible to set a dosage schedule that is suitable for all patients. To find the right dosage, follicle growth is checked by means of ultrasound scanning, and measurement of the amount of estradiol (female sex hormone) in blood.

Dosage in the male:

PUREGON[®] is usually prescribed at a dose of 450 IU per week, mostly given in 3 dosages of 150 IU per week **or** (also considered acceptable two dosages of 225 IU per week) both regimens given in combination with another hormone (hCG), for at least 3 to 4 months. Semen analysis is recommended 4 to 6 months after start of treatment to assess the response. If you have not responded after this period, your treatment may continue up to 48 weeks. Current clinical experience with other gonadotropins suggests that treatment for up to 18 months or longer may be necessary to achieve spermatogenesis.

How the injections are given: Using the pen, the injections are given slowly under the skin (for instance in the abdominal wall or in the upper thigh). The needle should be inserted at a 90° angle to the surface of the skin.

Using the solution for injection, flip - off the tamper - evident disc before insertion of the syringe needle. Tilt vial slightly before drawing up solution. The injections can be given under the skin or into a muscle. Your doctor will explain in more detail these two methods of injection.

To prevent painful injections and minimise leakage from the injection site, PUREGON[®] should be slowly administered intramuscularly or subcutaneously.

By whom: Using the solution in cartridges with the PUREGON PEN[®], injections just under the skin can be given by you or your partner. Your doctor will tell you when and how to do this. The first injection of PUREGON[®] should be given under medical supervision.

For women the PUREGON[®] solution for injection can be injected under the skin or into a muscle. Injections just under the skin can be given by you or your partner. The injections into a muscle should only be given by a doctor or nurse. For men the PUREGON[®] solution for injection can only be administered under the skin since injection into a muscle has not been investigated in this population. Your doctor will tell you when and how to inject. The first injection of PUREGON[®] should be given under medical supervision.

Overdose:

The acute toxicity of gonadotropins has been shown to be very low. Too high a dosage for more than one day may lead to hyperstimulation of the ovaries (OHSS).

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose contact your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following adverse reactions have been reported with gonadotropin therapy in general: mild to moderate ovarian enlargement; febrile reactions which may be associated with chills, musculoskeletal aches, joint pains, malaise, headache and fatigue; breast tenderness; dry skin; hair loss; hives; and hemoperitoneum.

The following reactions were observed during clinical trials; vaginitis, abdominal pain - upper/lower, nausea, abdominal discomfort, urinary tract infection, ovarian cyst, headache, vomiting, loose stools, faint feeling, laboured breathing, nasal congestion, sore throat, upper respiratory tract infection and nervousness.

The following adverse events have been reported subsequent to pregnancies resulting from gonadotropin therapy: tubal pregnancy; congenital abnormalities and birth defects. None of these events were considered drug-related and the incidence does not exceed that found in the general population. Spontaneous abortion was also observed in patients receiving urinary gonadotropin therapy. A slightly increased risk of multiple gestations has been seen.

The greatest concern your doctor will have is ovarian hyperstimulation syndrome (OHSS). To avoid the development of OHSS, your doctor will carefully

monitor your response to PUREGON[®]. Ovarian enlargement, sometimes accompanied by abdominal bloating may occur in about 20% of women taking gonadotropins. This is generally reversed with cessation of treatment and severe life-threatening cases are rare.

Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with ovarian hyperstimulation syndrome.

In the male: Common side effects (likely to affect 1 to 10 users in 100):

- Acne
- Hardening of the injection site
- Headache
- Rash
- Some breast development
- Testicular cyst

Clinical use of PUREGON[®] by the intramuscular or subcutaneous routes may lead to local reactions at the site of injection: bruising, pain, redness, swelling and itching, are commonly reported (3% of all patients treated). The majority of these local reactions are mild and transient in nature. Generalized hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.2% of all patients treated with PUREGON[®]).

Treatment of women

A complication with FSH treatment is unwanted overstimulation 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 follicle 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. The first symptoms of ovarian overstimulation may be noticed as pain in the stomach (abdomen), feeling sick or diarrhea. 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.

Contact your doctor without delay if you are experiencing any of these symptoms, also if they develop some days after the last injection has been given.

Common side effects (likely to affect 1 to 10 users in 100):

- 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 (likely to affect 1 to 10 users in 1,000)

- Breast complaints (including tenderness)
- Diarrhea, constipation or stomach discomfort
- Enlargement of the uterus
- Feeling sick
- 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 (likely to affect 1 to 10 users in 10,000)

- Blood clots (this may also occur in the absence of unwanted overstimulation of the ovaries).

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.

This is not a complete list of side effects. For any unexpected effects while taking PUREGON[®], contact your doctor or pharmacist immediately.

HOW TO STORE IT

Keep out of reach and sight of children. Do not use past expiry date. Protect from light.

Do not use if the solution contains particles or if the solution is not clear.

Patient: Store in a refrigerator (2°C - 8°C) (do not freeze) **or** store at or below 25°C for a maximum of 3 months (keep the cartridges or vials in the outer carton).

PUREGON[®] Solution for Injection in Cartridge:

Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days.

PUREGON[®] Solution for Injection in Vials:

The contents of a vial should be used immediately after piercing of the rubber stopper.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect[™] Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.organon.ca or by contacting the sponsor, Organon Canada Inc. at: 1-844-820-5468.

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