1. NAME OF THE MEDICINAL PRODUCT

Puregon solution for injection

150 IU/0.18 mL, 300 IU/0.36 mL, 600 IU/0.72 mL or 900 IU/1.08 mL.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One cartridge contains a net total dose of 150 IU, 300 IU, 600 IU or 900 IU recombinant follicle-stimulating hormone (FSH) in 0.18, 0.36, 0.72 or 1.08 ml aqueous solution. The solution for injection contains the active substance follitropin beta, produced by genetic engineering of a Chinese hamster ovary (CHO) cell line, in a concentration of 833 IU/mL aqueous solution. This strength corresponds to 83.3 microgram of protein / ml (specific *in vivo* bioactivity equal to approximately 10,000 IU FSH / mg protein).

Excipient(s) with known effect:

This medicinal product contains 10 mg of benzyl alcohol per mL. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless solution.

In cartridges, designed to be used in conjunction with a pen injector.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In the female:

Puregon is indicated for the treatment of female infertility in the following clinical situations:

- Anovulation (including polycystic ovarian syndrome, PCOS) in women who have been unresponsive to treatment with clomifene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs [e.g. *in vitro* fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)].

In the male

- Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

4.2 Posology and method of administration

Treatment with Puregon should be initiated under the supervision of a physician experienced in the treatment of fertility problems.

The first injection of Puregon should be performed under direct medical supervision.

Posology

Dosage in the female

There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasound assessment of follicular development. The concurrent determination of serum oestradiol levels may also be useful.

When using the pen-injector, it should be realised that the pen is a precision device which accurately delivers the dose to which it is set. It was shown that on average an 18% higher amount of FSH is given with the pen compared with a conventional syringe. This may be of particular relevance when switching between the pen-injector and a conventional syringe within one treatment cycle. Especially when switching from a syringe to the pen, small dose adjustments may be needed to prevent too high a dose being given.

Based on the results of comparative clinical studies, it is considered appropriate to give a lower total dosage of Puregon over a shorter treatment period than generally used for urinary FSH, not only in order to optimise follicular development but also to reduce the risk of unwanted ovarian hyperstimulation (see section 5.1).

Clinical experience with Puregon is based on up to three treatment cycles in both indications. Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

- Anovulation
  A sequential treatment scheme is recommended starting with daily administration of 50 IU Puregon. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol levels of 40-100% is considered to be optimal. The daily dose is then maintained until pre-ovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/mL (1,000-3,000 pmol/L) are attained. Usually, 7 to 14 days of treatment is sufficient to reach this state. The administration of Puregon is then discontinued and ovulation can be induced by administering human chorionic gonadotrophin (hCG).
  If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased. Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided to prevent multiple gestations.
- Controlled ovarian hyperstimulation in medically assisted reproduction programs
  Various stimulation protocols are applied. A starting dose of 100-225 IU is recommended for at least the first four days. Thereafter, the dose may be adjusted individually, based upon ovarian response. In clinical studies, it was shown that maintenance dosages ranging from 75-375 IU for six to twelve days are sufficient, although longer treatment may be necessary.
  Puregon can be given either alone, or, to prevent premature luteinisation, in combination with a GnRH agonist or antagonist. When using a GnRH agonist, a higher total treatment dose of Puregon may be required to achieve an adequate follicular response.
  Ovarian response is monitored by ultrasound assessment. The concurrent determination of serum oestradiol levels may also be useful. When ultrasound assessment indicates the presence of at least three follicles of 16-20 mm, and there is evidence of a good oestradiol response (plasma levels of about 300-400 picograms/mL (1,000-1,300 pmol/L) for each follicle with a diameter greater than 18 mm), the final phase of maturation of the follicles is induced by administration of hCG. Oocyte retrieval is performed 34-35 hours later.

Dosage in the male
Puregon should be given at a dosage of 450 IU/week, preferably divided in 3 dosages of 150 IU, concomitantly with hCG. Treatment with Puregon and hCG should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. To assess the response, semen analysis is recommended 4 to 6 months after the beginning of treatment. If a patient has not responded after this period, the combination therapy may be continued; current clinical experience indicates that treatment for up to 18 months or longer may be necessary to achieve spermatogenesis.

Paediatric population
There is no relevant use of Puregon in the paediatric population for the approved indication.

Method of administration
Puregon solution for injection in cartridges has been developed for use in the Puregon Pen and should be administered subcutaneously. The injection site should be alternated to prevent lipoatrophy.
Using the pen, injection of Puregon can be carried out by the patient or partner, provided that proper instructions are given by the physician. Before using the pen, the instructions for use must be read carefully.

4.3 Contraindications

For males and females
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Tumours of the ovary, breast, uterus, testis, pituitary or hypothalamus.
- Primary gonadal failure.

Additionally for females
- Undiagnosed vaginal bleeding.
- Ovarian cysts or enlarged ovaries, not related to polycystic ovarian syndrome (PCOS).
- Malformations of the reproductive organs incompatible with pregnancy.

- Fibroid tumours of the uterus incompatible with pregnancy.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Antibiotic hypersensitivity reactions

- Puregon may contain traces of streptomycin and/or neomycin. These antibiotics may cause hypersensitivity reactions in susceptible persons.

Infertility evaluation before starting treatment

- Before starting treatment, the couple's infertility should be assessed as appropriate. In particular, patients should be evaluated for hypothyroidism, adrenocortical insufficiency, hyperprolactinemia and pituitary or hypothalamic tumours, and appropriate specific treatment given.

In females

Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is a medical event distinct from uncomplicated ovarian enlargement. Clinical signs and symptoms of mild and moderate OHSS are abdominal pain, nausea, diarrhoea, mild to moderate enlargement of ovaries and ovarian cysts. Severe OHSS may be life-threatening. Clinical signs and symptoms of severe OHSS are large ovarian cysts, acute abdominal pain, ascites, pleural effusion, hydrothorax, dyspnoea, oliguria, haematological abnormalities and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS. Transient liver function test abnormalities suggestive of hepatic dysfunction with or without morphologic changes on liver biopsy have also been reported in association with OHSS.

OHSS may be caused by administration of human Chorionic Gonadotropin (hCG) and by pregnancy (endogenous hCG). Early OHSS usually occurs within 10 days after hCG administration and may be associated with an excessive ovarian response to gonadotropin stimulation. Late OHSS occurs more than 10 days after hCG administration, as a consequence of the hormonal changes with pregnancy. Because of the risk of developing OHSS, patients should be monitored for at least two weeks after hCG administration.

Women with known risk factors for a high ovarian response may be especially prone to the development of OHSS during or following treatment with Puregon. For women having their first cycle of ovarian stimulation, for whom risk factors are only partially known, close observation for early signs and symptoms of OHSS is recommended.

Follow current clinical practice for reducing the risk of OHSS during Assisted Reproductive Technology (ART). Adherence to the recommended Puregon dose and treatment regimen and careful monitoring of ovarian response is important to reduce the risk of OHSS. To monitor the risk of OHSS, ultrasonographic assessments of follicular development should be performed prior to treatment and at regular intervals during treatment; the concurrent determination of serum oestradiol levels may also be useful. In ART there is an increased risk of OHSS with 18 or more follicles of 11 mm or more in diameter.

If OHSS develops, standard and appropriate management of OHSS should be implemented and followed.

Multiple Pregnancy

Multiple pregnancies and births have been reported for all gonadotropin treatments, including Puregon. Multiple gestation, especially high order, carries an increased risk of adverse maternal (pregnancy and delivery complications) and perinatal (low birth weight) outcomes. For anovulatory women undergoing ovulation induction, monitoring follicular development with transvaginal ultrasonography may aid in determining whether or not to continue the cycle in order to reduce the risk of multiple pregnancies. The concurrent determination of serum oestradiol levels may also be useful. The patients should be advised of the potential risks of multiple births before starting treatment.

In women undergoing Assisted Reproduction Technologies (ART) procedures, the risk of a multiple pregnancy is mainly related to the number of embryos transferred. When used for an ovulation induction cycle, appropriate FSH dose adjustment(s) should prevent multiple follicle development.

Ectopic Pregnancy

Infertile women undergoing ART have an increased incidence of ectopic pregnancies. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.

Spontaneous Abortion
Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.

Vascular Complications
Thromboembolic events, both in association with and separate from OHSS, have been reported following treatment with gonadotropins, including Puregon. Intravascular thrombosis, which may originate in venous or arterial vessels, can result in reduced blood flow to vital organs or the extremities. In women with generally recognised risk factors for thromboembolic events, such as a personal or family history, severe obesity or thrombophilia, treatment with gonadotropins, including Puregon, may further increase this risk. In these women the benefits of gonadotropin administration, including Puregon, need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.

Congenital Malformations
The incidence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g., maternal age, sperm characteristics) and multiple gestations.

Ovarian Torsion
Ovarian torsion has been reported after treatment with gonadotropins, including Puregon. Ovarian torsion may be associated with other risk factors such as OHSS, pregnancy, previous abdominal surgery, past history of ovarian torsion, previous or current ovarian cyst and polycystic ovaries.
Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion.

Ovarian and other Reproductive System Neoplasms
There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple treatment regimens for infertility treatment. It is not established whether or not treatment with gonadotrophins increases the risk of these tumours in infertile women.

Other Medical Conditions
Medical conditions that contraindicate pregnancy should also be evaluated before starting treatment with Puregon.

In males

Primary Testicular Failure
Elevated endogenous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to Puregon/hCG therapy.

Benzyl alcohol
Benzyl alcohol may cause anaphylactoid reactions.
Large amounts of benzyl alcohol may cause metabolic acidosis. Special precautions should be taken when prescribing Puregon to pregnant or breast-feeding women and patients with liver or kidney disease.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per injection, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of Puregon and clomifene citrate may enhance the follicular response. After pituitary desensitisation induced by a GnRH agonist, a higher dose of Puregon may be necessary to achieve an adequate follicular response.

4.6 Fertility, pregnancy and lactation

Fertility
Puregon is used in the treatment of women undergoing ovarian induction or controlled ovarian hyperstimulation in assisted reproduction programmes. In males Puregon is used in the treatment of deficient

spermatogenesis due to hypogonadotrophic hypogonadism. For posology and method of administration, see section 4.2.

Pregnancy
The use of Puregon during pregnancy is not indicated. In case of inadvertent exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Breast-feeding
There is no information available from clinical or animal studies on the excretion of follitropin beta in milk. It is unlikely that follitropin beta is excreted in human milk due to its high molecular weight. If follitropin beta would be excreted in human milk, it would be degraded in the gastrointestinal tract of the child. Follitropin beta may affect milk production.

4.7 Effects on ability to drive and use machines

Puregon has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Clinical use of Puregon by the intramuscular or subcutaneous routes may lead to local reactions at the site of injection (3% of all patients treated). The majority of these local reactions are mild and transient in nature. Generalised hypersensitivity reactions have been observed uncommonly (approximately 0.2% of all patients treated with follitropin beta). Cases of anaphylactic reactions (including those requiring hospitalisation) have been reported in the post-marketing setting.

Treatment of females:
In approximately 4% of the women treated with follitropin beta in clinical trials, signs and symptoms related to ovarian hyperstimulation syndrome (OHSS) have been reported (see section 4.4). Adverse reactions related to this syndrome include pelvic pain and/or congestion, abdominal pain and/or distension, breast complaints and ovarian enlargement.

The table below lists the adverse reactions with follitropin beta reported in clinical trials and post-marketing surveillance in females, according to system organ class and frequency; common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and not known (cannot be estimated from available data).

SOC	Frequency	Adverse reaction
Immune system disorders	Not known	Anaphylactic reactions
Nervous system disorders	Common	Headache
Gastrointestinal disorders	Common	Abdominal distension Abdominal pain
	Uncommon	Abdominal discomfort Constipation Diarrhoea Nausea
Reproductive system and breast disorders	Common	OHSS Pelvic pain
	Uncommon	Breast complaints[1] Metrorrhagia Ovarian cyst Ovarian enlargement Ovarian torsion Uterine enlargement Vaginal haemorrhage
General disorders and administration site conditions	Common	Injection site reaction[2]

	Uncommon	Generalised hypersensitivity reaction[3]

1. Breast complaints include tenderness, pain and/or engorgement and nipple pain
2. Local reactions at the site of injection include: bruising, pain, redness, swelling and itching
3. Generalised hypersensitivity reaction include erythema, urticaria, rash and pruritus

In addition, ectopic pregnancy, miscarriage and multiple gestations have been reported. These are considered to be related to ART or subsequent pregnancy.
In rare instances, thromboembolism has been associated with follitropin beta / hCG therapy as with other gonadotrophins.

Treatment of males:
The table below lists the adverse reactions with follitropin beta reported in a clinical trial in males (30 patients dosed) and post-marketing surveillance, according to system organ class and frequency; common (≥ 1/100 to < 1/10) and not known (cannot be estimated from available data).

SOC	**Frequency[1]**	**Adverse reaction**
Immune system disorders	Not known	Anaphylactic reactions
Nervous system disorders	Common	Headache
Skin and subcutaneous tissue disorders	Common	Acne Rash
Reproductive system and breast disorders	Common	Epididymal cyst Gynaecomastia
General disorders and administration site conditions	Common	Injection site reaction[2]

1. Adverse reactions that are reported only once are listed as common because a single report raises the frequency above 1%.
2. Local reactions at the site of injection include induration and pain.

Side effects can be reported to the Ministry of Health by using the online form for reporting side effects in the homepage of the ministry of health website www.health.gov.il or by entering the following link: https://sideeffects.health.gov.il

4.9 Overdose

No data on acute toxicity of Puregon in humans is available, but the acute toxicity of Puregon and of urinary gonadotrophin preparations in animal studies has been shown to be very low. Too high a dosage of FSH may lead to hyperstimulation of the ovaries (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system, gonadotrophins; ATC code: G03G A06.

Puregon contains a recombinant FSH. This is produced by recombinant DNA technology, using a Chinese hamster ovary cell line transfected with the human FSH subunit genes. The primary amino acid sequence is identical to that of natural human FSH. Small differences in the carbohydrate chain structure are known to exist.

Mechanism of Action
FSH is indispensable in normal follicular growth and maturation, and gonadal steroid production. In the female the level of FSH is critical for the onset and duration of follicular development, and consequently for the timing and number of follicles reaching maturity. Puregon can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore, Puregon can be used to promote multiple follicular development in medically assisted reproduction programs [e.g. *in*

vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)]. Treatment with Puregon is generally followed by administration of hCG to induce the final phase of follicle maturation, resumption of meiosis and rupture of the follicle.

Clinical Efficacy and Safety
In clinical studies comparing recFSH (follitropin beta) and urinary FSH for controlled ovarian stimulation in women participating in an assisted reproduction technology (ART) program and for ovulation induction (see tables 1 and 2 below), Puregon was more potent than urinary FSH in terms of a lower total dose and a shorter treatment period needed to trigger follicular maturation.

For controlled ovarian stimulation, Puregon resulted in a higher number of oocytes retrieved at a lower total dose and with a shorter treatment period, when compared to urinary FSH.

Table 1: Results of study 37,608 (randomized, group comparative clinical study comparing safety and efficacy of Puregon with urinary FSH in controlled ovarian stimulation).

	Puregon (n = 546)	**u-FSH (n = 361)**
Mean no. of oocytes retrieved	10.84*	8.95
Mean total dose (no. of 75 IU ampoules)	28.5*	31.8
Mean duration of FSH stimulation (days)	10.7*	11.3

* Differences between the 2 groups were statistically significant ($p<0.05$).

For ovulation induction, Puregon resulted in a lower median total dose and shorter median duration of treatment when compared to urinary FSH.

Table 2: Results of study 37,609 (randomized, group comparative clinical study comparing safety and efficacy of Puregon with urinary FSH in ovulation induction).

		Puregon (n = 105)	**u-FSH (n = 66)**
Mean no. of follicles	≥ 12 mm	3.6*	2.6
	≥ 15 mm	2.0	1.7
	≥ 18 mm	1.1	0.9
Median total dose (IU)[a]		750*	1,035
Median duration of treatment (days)[a]		10.0*	13.0

* Differences between the 2 groups were statistically significant ($p<0.05$).
[a] Restricted to women with ovulation induced (Puregon, n = 76; u-FSH, n = 42).

5.2 Pharmacokinetic properties

Absorption
After subcutaneous administration of Puregon, maximum concentration of FSH is reached within about 12 hours. Due to the sustained release from the injection site and the elimination half-life of about 40 hours (ranging from 12 to 70 hours), FSH levels remain increased for 24-48 hours. Due to the relatively long elimination half-life, repeated administration of the same dose will lead to plasma concentrations of FSH that are approximately 1.5-2.5 times higher than after single-dose administration. This increase enables therapeutic FSH concentrations to be reached.
The absolute bioavailability of subcutaneously administered Puregon is approximately 77%.

Distribution, biotransformation and elimination
Recombinant FSH is biochemically very similar to urinary human FSH and is distributed, metabolised, and excreted in the same way.

5.3 Preclinical safety data

Single-dose administration of Puregon to rats induced no toxicologically significant effects. In repeated-dose studies in rats (two weeks) and dogs (13 weeks) up to 100-fold the maximal human dose, Puregon induced

no toxicologically significant effects. Puregon showed no mutagenic potential in the Ames test and in the *in vitro* chromosome aberration test with human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Puregon solution for injection contains:
Sucrose
Sodium citrate
Benzyl alcohol
L-methionine
Polysorbate 20
Water for injections
The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days.

6.4 Special precautions for storage

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.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Boxes of Puregon solution for injection contain 1 cartridge of Puregon and 3 (150 IU cartridges), 6 (300 IU and 600 IU cartridges) or 9 (900 IU cartridges) needles to be used with the Puregon Pen.
The cartridges are of type 1 borosillicate tube glass, with a rubber piston and an aluminium crimp-cap with a rubber inlay.
Cartridges contain 833 IU of FSH activity per mL aqueous solution. Cartridges with a net dose of 150 IU contain a minimum of 225 IU in 0.270 mL; those of 300 IU contain a minimum of 400 IU in 0.480 mL; those of 600 IU contain a minimum of 700 IU in 0.840 mL; those of 900 IU contain a minimum of 1025 IU in 1.230 mL.
Not all pack sizes may be marketed.

6.6 Special precautions for handling and disposal

Do not use if the solution contains particles or if the solution is not clear.
Puregon solution for injection is designed for use in conjunction with the Puregon Pen. The instructions for using the pen must be followed carefully.
Air bubbles must be removed from the cartridge before injection (see instructions for using the pen).
A small amount of Puregon solution for injection may remain in the cartridge after completion of treatment with Puregon even when all doses have been correctly given. Patients should be instructed not to try to use the remaining Puregon solution for injection, but to properly discard the cartridge.
Empty cartridges must not be refilled.
Puregon cartridges are not designed to allow any other drug to be mixed in the cartridges.
Discard used needles immediately after injection.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Organon LLC, NJ USA

8. LICENSE HOLDER AND ADDRESS

Organon Pharma Israel Ltd., 1 Atir Yeda, Kfar Saba

9. REGISTRATION NUMBER

130.52.30898

Revised in April 2024.