ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Puregon 300 IU/0.36 mL solution for injection
Puregon 600 IU/0.72 mL solution for injection
Puregon 900 IU/1.08 mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Puregon 300 IU/0.36 mL solution for injection
One cartridge contains a net total dose of 300 IU recombinant follicle-stimulating hormone (FSH) in 0.36 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).

Puregon 600 IU/0.72 mL solution for injection
One cartridge contains a net total dose of 600 IU recombinant follicle-stimulating hormone (FSH) in 0.72 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).

Puregon 900 IU/1.08 mL solution for injection
One cartridge contains a net total dose of 900 IU recombinant follicle-stimulating hormone (FSH) in 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (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 adult females:
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 adult males:
- 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 with 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, 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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
L-methionine
Polysorbate 20
Benzyl alcohol
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

3 years.

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.
Keep the cartridge in the outer carton.
For patient convenience, Puregon may be stored at or below 25ºC by the patient for a single period of not more than 3 months.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Puregon 300 IU/0.36 mL solution for injection
0.36 mL of solution in 1.5 mL cartridge (type I glass) with a grey rubber piston and an aluminium crimp-cap with a rubber inlay.
Pack of 1 cartridge and 6 needles to be used with the Puregon Pen.
Cartridges contain a minimum of 400 IU FSH activity in 0.480 mL aqueous solution, which is sufficient for a net total dose of 300 IU.

Puregon 600 IU/0.72 mL solution for injection
0.72 mL of solution in 1.5 mL cartridge (type I glass) with a grey rubber piston and an aluminium crimp-cap with a rubber inlay.
Pack of 1 cartridge and 6 needles to be used with the Puregon Pen.
Cartridges contain a minimum of 700 IU FSH activity in 0.840 mL aqueous solution, which is sufficient for a net total dose of 600 IU.

Puregon 900 IU/1.08 mL solution for injection
1.08 mL of solution in 1.5 mL cartridge (type I glass) with a grey rubber piston and an aluminium crimp-cap with a rubber inlay.
Pack of 1 cartridge and 9 needles to be used with the Puregon Pen.
Cartridges contain a minimum of 1,025 IU FSH activity in 1.230 mL aqueous solution, which is sufficient for a net total dose of 900 IU.

6.6 Special precautions for disposal and other handling

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. MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

8. MARKETING AUTHORISATION NUMBER

Puregon 300 IU/0.36 mL solution for injection
EU/1/96/008/038

Puregon 600 IU/0.72 mL solution for injection
EU/1/96/008/039

Puregon 900 IU/1.08 mL solution for injection
EU/1/96/008/041

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 03 May 1996
Date of latest renewal: 29 May 2006

10. DATE OF REVISION OF THE TEXT

DD month YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

N.V. Organon
Kloosterstraat 6, 5349 AB Oss
Vollenhovermeer 2 5347 JV Oss
The Netherlands

Name and address of the manufacturer responsible for batch release

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT Puregon 300 IU/0.36 mL 1 cartridge

1. NAME OF THE MEDICINAL PRODUCT

Puregon 300 IU/0.36 mL solution for injection
follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

400 IU recombinant FSH activity/0.480 mL
Net content 300 IU

3. LIST OF EXCIPIENTS

Other ingredients: sucrose, sodium citrate, L-methionine, polysorbate 20 and benzyl alcohol in water for injections; sodium hydroxide and/or hydrochloric acid as pH adjustment.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 cartridge
2 packs with 3 pen needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous (SC) use
For use only with the Puregon Pen.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

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

9. SPECIAL STORAGE CONDITIONS

Storage by the pharmacist
Store at 2°C - 8°C (in a refrigerator). Do not freeze.

Storage by the patient
You have two options:
1. Store at 2°C – 8°C (in a refrigerator). Do not freeze.
2. Store at or below 25°C for a single period of not more than 3 months.
Keep the cartridge in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER

EU/1/96/008/038

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE TEXT Puregon 300 IU/0.36 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Puregon 300 IU/0.36 mL injection
follitropin beta

SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.480 mL

6. OTHER

Organon

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT Puregon 600 IU/0.72 mL 1 cartridge

1. NAME OF THE MEDICINAL PRODUCT

Puregon 600 IU/0.72 mL solution for injection
follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

700 IU recombinant FSH activity/0.840 mL
Net content 600 IU

3. LIST OF EXCIPIENTS

Other ingredients: sucrose, sodium citrate, L-methionine, polysorbate 20 and benzyl alcohol in water for injections; sodium hydroxide and/or hydrochloric acid as pH adjustment.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 cartridge
2 packs with 3 pen needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous (SC) use
For use only with the Puregon Pen.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

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

9. SPECIAL STORAGE CONDITIONS

Storage by the pharmacist
Store at 2°C - 8°C (in a refrigerator). Do not freeze.

Storage by the patient
You have two options:
1. Store at 2°C – 8°C (in a refrigerator). Do not freeze.
2. Store at or below 25°C for a single period of not more than 3 months.
Keep the cartridge in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER

EU/1/96/008/039

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE TEXT Puregon 600 IU/0.72 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Puregon 600 IU/0.72 mL injection
follitropin beta

SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.840 mL

6. OTHER

Organon

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT Puregon 900 IU/1.08 mL 1 cartridge

1. NAME OF THE MEDICINAL PRODUCT

Puregon 900 IU/1.08 mL solution for injection
follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1025 IU recombinant FSH activity/1.230 mL
Net content 900 IU

3. LIST OF EXCIPIENTS

Other ingredients: sucrose, sodium citrate, L-methionine, polysorbate 20 and benzyl alcohol in water for injections; sodium hydroxide and/or hydrochloric acid as pH adjustment.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 cartridge
3 packs with 3 pen needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous (SC) use
For use only with the Puregon Pen.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

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

9. SPECIAL STORAGE CONDITIONS

Storage by the pharmacist
Store at 2°C - 8°C (in a refrigerator). Do not freeze.

Storage by the patient
You have two options:
1. Store at 2°C – 8°C (in a refrigerator). Do not freeze.
2. Store at or below 25°C for a single period of not more than 3 months.
Keep the cartridge in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE TEXT Puregon 900 IU/1.08 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Puregon 900 IU/1.08 mL injection
follitropin beta

SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.230 mL

6. OTHER

Organon

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Puregon 300 IU/0.36 mL solution for injection
Puregon 600 IU/0.72 mL solution for injection
Puregon 900 IU/1.08 mL solution for injection
follitropin beta

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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Puregon is and what it is used for

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

FSH belongs to the group of gonadotrophins, 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.

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.

2. What you need to know before you use Puregon

Do not use Puregon

If you:
- are allergic to follitropin beta or any of the other ingredients of Puregon (listed in section 6)
- 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.

Warnings and precautions

Talk to your doctor before using Puregon 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 build-up, diarrhoea, decreased urine output or trouble breathing (see also section 4 on Possible 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 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.

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 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.

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.

Children and adolescents
There is no relevant use of Puregon in children and adolescents.

Other medicines and Puregon

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

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.

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.

Driving and using machines

Puregon is unlikely to affect your ability to drive or use machines.

Puregon contains benzyl alcohol

This medicinal product contains 10 mg of benzyl alcohol per mL.
Benzyl alcohol may cause allergic reactions.
Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").
Ask your doctor or pharmacist for advice 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").

Puregon contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per injection, that is to say essentially 'sodium-free'.

3. How to use Puregon

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

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.

How are the injections given

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.
The very first injection of Puregon should only be given in the presence of a doctor or nurse.
A small amount of the medicine may remain in the cartridge after the treatment with Puregon is completed even when all doses have been correctly given. Do not try to use any remaining medicine. After administration of the last dose, the cartridge must be properly discarded.

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 on possible side effects.

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.

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

4. Possible side effects

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

Tell your doctor straight away if you notice:
Signs of a serious allergic reaction (anaphylactic reaction) such as swelling of the face, lips, throat or tongue which makes it difficult to swallow or breathe, shortness of breath, feeling of loss of consciousness.

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 warnings and precautions in section 2.
→ 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
- 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 warnings and precautions in section 2)

Not known side effects (cannot be estimated from the available data):
- Allergic reactions:
  - swelling of the face, lips, throat or tongue which makes it difficult to swallow or breathe, shortness of breath
  - pale skin, a weak and rapid pulse or a feeling of loss of consciousness

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

Not known side effects (cannot be estimated from the available data):
- Allergic reactions:
  - swelling of the face, lips, throat or tongue which makes it difficult to swallow or breathe, shortness of breath
  - pale skin, a weak and rapid pulse or a feeling of loss of consciousness

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Puregon

Keep this medicine out of the sight and reach of children.

Storage by the pharmacist
Store at 2°C – 8°C (in a refrigerator). Do not freeze.

Storage by the patient
You have two options:
1. Store at 2°C – 8°C (in a refrigerator). Do not freeze.

2. Store at or below 25ºC (at room temperature) for a single period of not more than 3 months. Make a note of when you start storing the product out of the refrigerator.

Keep the cartridge in the outer carton.

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.
Do not use Puregon after the expiry date which is stated on the label and carton after 'EXP'. The expiry date refers to the last day of that month.

Discard used needles immediately after injection.
Do not mix any other drug into the cartridges. Empty cartridges must not be refilled.

Do not throw away any medicines via wastewater or household waste. 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 Puregon contains

- Each cartridge contains the active substance follitropin beta, a hormone known as follicle-stimulating hormone (FSH) in a strength of 833 IU/mL aqueous solution.
- The other ingredients are 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.

What Puregon looks like and contents of the pack

Puregon solution for injection (injection) is a clear, colourless liquid. It is supplied in a glass cartridge. It is available in packs of 1 cartridge.

Marketing Authorisation Holder and Manufacturer
N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.