PUREGON ®
Solution for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

Puregon *solution for injection* contains the active substance recombinant follicle-stimulating hormone (FSH) (follitropin beta).
One vial of Puregon *solution for injection* contains 50 or 100 IU FSH activity in 0,5 ml aqueous solution. This corresponds to strengths of 100 or 200 IU/ml. One vial contains 5 or 10 microgram of protein respectively (specific in vivo bioactivity equal to approximately 10.000 IU FSH / mg protein).

For excipients: see *'List of excipients'*

PHARMACEUTICAL FORM

Solution for injection

CLINICAL PARTICULARS

Therapeutic indications

In the female:

Puregon is indicate for the treatment of female infertility in the following clinical situation:

- Puregon is recommended for the stimulation of follicular development and ovulation in women with hypothalamic-pituitary dysfunction who present with either oligomenorrhoea or amenorrhoea. These women are classified as WHO group II patients and usually receive clomiphene citrate as primary therapy. They have evidence of endogenous oestrogen production and thus will either spontaneously menstruate or experience withdrawal bleeding after progestogen administration. Polycystic ovarian disease (PCOD) is part of WHO II classification and is present in the majority of these patients.
- Puregon is indicated for stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilization (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT).

In the male:

Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

Posology and method of administration

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

Posology

Dosage in 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 ultrasonography and monitoring of oestradiol levels. In comparative clinical studies with Puregon and urinary FSH it was shown that Puregon is more effective than urinary FSH in terms of lower total dose and a shorter treatment period needed to achieve pre-ovulatory conditions. Therefore, it is considered appropriate to give a lower dosage of Puregon than generally used for urinary FSH, not only in order to optimize follicular development but also to minimise the risk of unwanted ovarian hyperstimulation.
Puregon can be given either alone, or in combination with a GnRH analogue to prevent premature luteinisation. In the latter case, especially when using a GnRH agonist, a higher total treatment dose of Puregon may be required to achieve an adequate follicular response.
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 percent is considered to be optimal. The daily dose is then maintained until preovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at leat 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/ml (1000-3000 pmol/L) are attained. Ussualy, 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 in order 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 or 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 ultrasonography and measurement of plasma oestradiol levels. When ultrasonographic evaluation 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 picogram/ml (1000-1300 pmol/l) for each follicle with a diameter greater than 18mm), the final phase of maturation of the follicles is induced by administration of hCG.

Oocyte retrieval is performed 34-35 hours later.

Dosage in male:
Puregon should be given at dosage of 450 IU/week, preferably divided in 3 dosages of 150 IU, concomitantly with hCG. The treatment should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. 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.

Method of administration
To prevent painful injections and minimize leakage from the injection site Puregon should be slowly administered intramuscularly or subcutaneously. The subcutaneous injection site should be alternated to prevent lipoathrophy. Any unused solution should be discarded.
Subcutaneous injection of Puregon may be carried out by patient or partner, provided that proper instructions are given by the physician. Self administration of Puregon should only be performed by patients who are well-motivated, adequately trained and with access to expert advice.

Contraindications

- Tumours of the ovary, breast, uterus, pituitary or hypothalamus
- Pregnancy or lactation
- Undiagnosed vaginal bleeding
- Hypersensitivity to the active substance or to any of the excipients
- Primary ovarian failure
- Ovarian cysts or enlarged ovaries, not related to polycystic ovarian disease (PCOD)
- Malformations of the sexual organs incompatible with pregnancy
- Fibroid tumours of the uterus incompatible with pregnancy
- Primary testicular failure

Special warnings and special precautions for use

- The presence of uncontrolled non-gonodal endocrinopathies (e.g. thyroid, adrenal or pituitary disorders) should be excluded
- In pregnancies occurring after induction of ovulation with gonadotrophin preparations, there is an increased risk of multiple gestations
- There has been no reports of hypersensitivity to Puregon, but there remains the possibility of anaphylactic responses
- The first injection of Puregon should be performed under direct medical supervision
- Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
- Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.
- *Unwanted ovarian hyperstimulation*
  In the treatment of female patients, ultrasonographic assessment of follicular development, and determination of oestradiol levels should be performed prior to treatment and at regular

intervals during treatment. Apart from the development of a high number of follicles, oestradiol levels may rise very rapidly, e.g. more than a daily doubling for two or three consecutive days, and possibly reaching excessively high values. The diagnosis of ovarian hyperstimulation may be confirmed by ultrasound examination. If this unwanted ovarian hyperstimulation occurs (i.e. not as part of controlled ovarian hyperstimulation in medically assisted reproduction programs), the administration of Puregon should be discontinued. In that case pregnancy should be avoided and hCG must be withheld, because it may induce, in addition to multiple ovulation, the ovarian hyperstimulation syndrome (OHSS). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.

- Women with generally, recognized risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m2) or established thrombophilia, may have an increased risk of venous or arterial thrombo-embolic processes upon treatment with gonadotrophins, even without concurrent OHSS. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
- Elevated endogenous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to Puregon/hCG therapy.
- In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.

Interaction with other medicinal products and other forms of interaction
Concomitant use of Puregon and clomiphene 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.

Pregnancy and lactation
Puregon must not be used during pregnancy and lactation.

Effects on ability to drive and use machines
No effects on ability to drive and use machines have been observed.

Undesirable effects

Clinical use of Puregon by the intramuscular or subcutaneous routes may lead to reactions at the site of injection such as bruising, pain, redness, swelling and itching, the majority of which are mild and transient in nature. Very rarely, generalized reactions including erythema and rash have been observed. Formation of antibodies against follitropin beta or host cell derived proteins have not been observed during therapy.

Treatment of women
Unwanted ovarian hyperstimulation has been observed in 5% of subjects treated with Puregon. Characteristic symptoms of these conditions have been described (see *"Special warnings and special precautions for use"*).

A slightly increased risk of ectopic pregnancy and multiple pregnancies has been seen.
In rare instances, thromboembolism has been associated with other gonadotrophins therapy. This may also occur with Puregon/hCG therapy.

Treatment of men
Gynaecomastia and acne may occur occasionally during Puregon/hCG therapy.
These are known effects of hCG treatment.

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 "*Unwanted ovarian hyperstimulation*")

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group: 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.
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 fertilization/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.

Pharmacokinetic properties
After intramuscular or subcutaneous administration of Puregon, maximum concentrations of FSH are 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 remains 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.
There are no significant pharmacokinetic differences between intramuscular and subcutaneous administration of Puregon. Both have an absolute bioavailability of approximately 77 per cent. Recombinant FSH is biochemically very similar to urinary human FSH and is distributed, metabolized, and excreted in the same way.

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

PHARMACEUTICAL PARTICULARS

List of excipients
Puregon *solution for injection* contains sucrose, sodium citrate, L-methionine and polysorbate 20 in water for injections. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

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

Shelf-life
3 years

Special precautions for storage
Storage by the pharmacist

Store at 2°C-8°C (in refrigerator). Do not freeze.

Storage by the patient

There are two options:

1. Store at 2°C-8°C (in refrigerator). Do not freeze.
2. Store at or below 25°C for single period of not more than 3 months.

Keep the container in the outer carton.

Nature and contents of containers
Boxes of Puregon *solution for injection* contain 1 or 5 vial(s) of follitropin beta in 0,5 ml aqueous solution. Puregon *solution for injection* is filled in colourless, 3 ml injection vials of hydrolytic resistant glass, Type I, and closed with chlorobutyl rubber closures.

Box of 1 vial 50 IU	Reg. No. : DKI 0464802243 A1
Box of 5 vials 50 IU	Reg. No. : DKI 0464802243 A1
Box of 10 vials 50 IU	Reg. No. : DKI 0464802243 A1
Box of 1 vial 100 IU	Reg. No. : DKI 0464802243 C1
Box of 5 vials 100 IU	Reg. No. : DKI 0464802243 C1
Box of 10 vials 100 IU	Reg. No. : DKI 0464802243 C1

N.B. Not all the above-mentioned presentations may be available in this country

Instructions for use, handling and disposal
Do not use if the solution contains particles or if the solution is not clear.
The contents of vial should be used immediately after piercing of the rubber stopper.

Discard any remaining solution after single use.

Instruction for use

Step 1 – Preparing the syringe
Sterile disposable syringes and needles should be used for administration of Puregon. The volume of the syringe should be small enough so that the prescribed dose can be given reasonable accuracy.
Puregon solution for injection comes in glass vial. Do not use if the solution contains particles or is not clear. First, remove the flip-off cap of the vial. Place a needle on a syringe and pierce the needle through the rubber stopper of the vial (a).
Draw the solution up into the syringe (b), and replace the needle with an injection needle (c). Finally hold the syringe with the needle pointing upwards and gently tap the side to force any air bubbles up to the top; then squeeze the plunger until all the air has been expelled, and only Puregon solution is left in the syringe (d). If necessary, the plunger may be squeezed further, to adjust the volume to be administered.

Step 2 – The injection site
The best site for subcutaneous injection is in the abdomen around the navel (e) where there is a lot of loose skin and layers of fatty tissue. You should vary the injection site a little with each injection.
It is possible to inject in other areas. Your doctor or nurse will advise you where to inject.

Step 3 – Preparing the area
A few taps at the injection site will stimulate tiny nerve endings and help reduce discomfort when the needle goes in. Hands should be washed and the injection site swabbed with disinfectant (for example chlorohexidine 0,5%) to remove any surface bacteria. Clean about two inches around the point where the needle will go in and let the disinfectant dry for at least one minute before proceeding.

Step 4 – Inserting the needle
Pinch the skin a little. With the other hand, insert the needle at an angle of 90 degrees into the skin's surface (f).

Step 5 – Checking the correct needle position
If the needle position is correct the plunger should be quite difficult to draw back. Any blood sucked back into the syringe means that the needle tip has penetrated a vein or artery. If this happens pull out the syringe, cover the injection site with a swab containing disinfectant and apply pressure; the site will stop bleeding in a minute or two. Do not use this solution but flush it away. You should then start again with Step 1 using a new needle and syringe and a new vial of Puregon.

Step 6 – injecting the solution
Depress the plunger **slowly** and steadily, so the solution is correctly injected and the skin tissues are not damaged.

Step 7 – Removing the syringe
Pull the syringe out quickly and apply pressure to the injection site with a swab containing

disinfectant. A gentle massage of the site – while still maintaining pressure – helps disperse the Puregon solution and relieve any discomfort.

In correspondence please quote the packing number.

ON DOCTOR'S PRESCRIPTION ONLY
Harus dengan resep dokter

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