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RU M2530.031.101

Puregon

injection

Composition

Puregon consists of a freeze-dried powder and a solvent for reconstitution. The powder for injection contains the active ingredient recombinant follicle-stimulating hormone (FSH) (proposed INN follitropin beta).
One container of Puregon contains 50, 100 or 150 I.U. FSH activity corresponding to 5, 10 or 15 microgram of protein (specific in vivo bioactivity equal to approximately 10 000 I.U. FSH / mg protein[1]). Puregon is in the form of a lyophilised sphere or lyosphere.
N.B. Not all of the above-mentioned concentrations may be available in this country.

[1] as determined by the Ph.Eur. test for FSH in vivo bioactivity and on the basis of the molar extinction coefficient at 277 nm (ε_s; $mg^{-1}cm^{-1}$) = 1.066.

Characteristics

Pharmacodynamic properties

(atc classification: gonadotrophins, G03G A)
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 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.

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 remain increased for 24-48 hours. Due to the relatively long elimination half-life,

Posology

There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotropins. 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 estradiol levels. After pituitary desensitisation induced by a GnRH agonist a higher dose of Puregon may be necessary 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 the treatment success rate remains stable during the first 4 attempts and gradually declines thereafter.

- *Anovulation*
  In general, a sequential treatment scheme is recommended. This usually starts with daily administration of 75 I.U. FSH activity. 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 estradiol levels indicate an adequate pharmacodynamic response. A daily increase of estradiol levels of 40-100 per cent 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 estradiol levels of 300-900 picograms/mL (1000-3000 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 gonadotropin (hCG).
  If the number of responding follicles is too high or estradiol levels increase too rapidly, i.e. more than a daily doubling for estradiol 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 150-225 I.U. is recommended for at least the first

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, metabolised, and excreted in the same way.

Indications

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

- Anovulation (including polycystic ovarian disease, PCOD), in women who have been unresponsive to treatment with clomiphene 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)].

Dosage and administration

General

The dosage recommendations given below are in line with those usually applied for urinary FSH. These dosages were also applied in comparative clinical studies with Puregon and urinary FSH. In these studies it was shown that Puregon is more effective than urinary FSH in terms of a lower total dose and a shorter treatment period needed to achieve pre-ovulatory conditions. Therefore, it may be appropriate to give a lower dosage of Puregon than for urinary FSH. This advice is not only relevant in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation. For this purpose the dosage range of Puregon includes the strengths of 50 I.U. and 100 I.U.

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 I.U. for six to twelve days are sufficient, although longer treatment may be necessary.

Puregon can be given either alone, or in combination with a GnRH agonist to prevent premature luteinisation. In the latter case a higher total treatment dose of Puregon may be required.

Ovarian response is monitored by ultrasonography and measurement of plasma estradiol levels. When ultrasonographic evaluation indicates the presence of at least three follicles of 16-20 mm, and there is evidence of a good estradiol response (plasma levels of about 300-400 picogram/mL (1000-1300 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.

Method of administration

Puregon should be reconstituted with the solvent provided. The reconstituted solution should be administered immediately.

To prevent painful injections and minimise leakage from the injection site the Puregon solution should be slowly administered intramuscularly or subcutaneously. The subcutaneous injection site should be alternated to prevent lipoatrophy. 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 ovary, breast, uterus, pituitary or hypothalamus.
- Pregnancy or lactation.
- Undiagnosed vaginal bleeding.

- Hypersensitivity to any of the substances in Puregon.
- 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.

Warnings and precautions

- The presence of uncontrolled non-gonadal endocrinopathies (e.g. thyroid, adrenal or pituitary disorders) should be excluded.
- In pregnancies occurring after induction of ovulation with gonadotropic preparations, there is an increased risk of multiple gestations.
- There have been no reports of hypersensitivity to Puregon, but there remains the possibility of anaphylactic responses. The first injection of Puregon should only 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 ART are higher than in the normal population.
- *Unwanted ovarian hyperstimulation*
In the treatment of female patients, ultrasonographic assessment of follicular development, and determination of estradiol levels should be performed prior to treatment and at regular intervals during treatment. Apart from the development of a high number of follicles, estradiol 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. 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, arterio-thromboembolic processes have been associated with other gonadotropin therapy. This may also occur with Puregon/hCG.

Adverse reactions

Unwanted ovarian hyperstimulation has been observed in 5% of subjects treated with Puregon. Characteristic symptoms of this condition have been described (see 'special warnings and special precautions for use').
Clinical use of Puregon by the IM or SC routes may lead to reactions at the site of injection, such as bruising, pain, redness, swelling and itching, the majority of which are mild. Generalised reactions have not been observed.
Formation of antibodies against follitropin beta or host cell-derived proteins have not been observed during therapy.
A slightly increased risk of ectopic pregnancy and multiple gestations has been seen. In rare instances, arterio-thromboembolisms have been associated with menotropin/human chorionic gonadotropin therapy. This may also occur with Puregon/hCG therapy.

Interactions

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.

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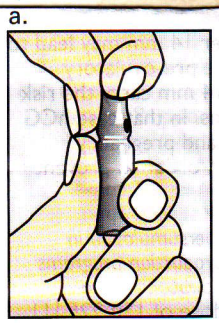

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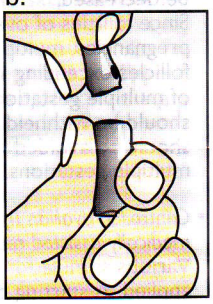

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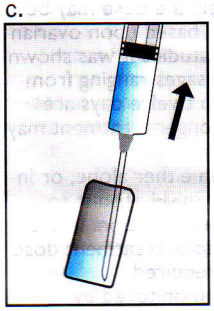

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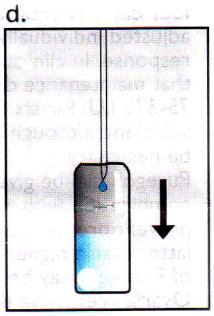

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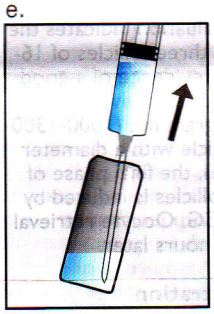

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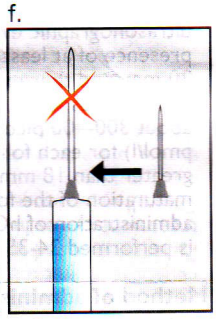

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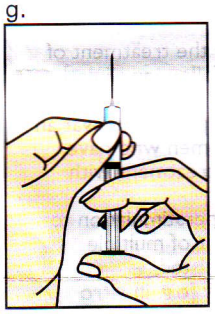

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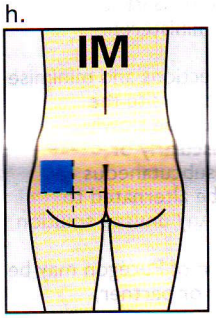

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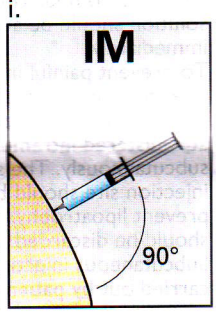

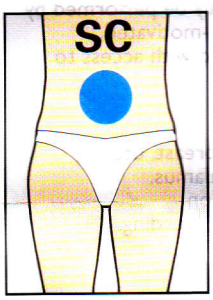

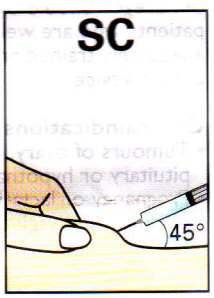

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Effects on ability to drive and use machines
As far as known this medicine has no influence on alertness and concentration.

Overdosage
No data on acute toxicity of Puregon in humans is available, but the acute toxicity of Puregon and of urinary gonadotropin 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, Special warnings and precautions for use).

In correspondence please quote packing number.

a) Break off the top, by holding the ampoule firmly in one hand,
b) Press the thumb of your other hand on the top chamber, while tilting the top chamber backwards with your finger as indicated in the figure.
c) Draw up the solvens in the syringe.

d) Insert the solvens in the ampoule with the Puregon sphere.
e) Now, draw up the Puregon solution into the syringe again.
f) Attach a new sterile needle for injection.
g) Flick the syringe gently and press the plunger, with the needle in an upward position, to force out the air till a drop shows at the tip of the needle.

IM injection
h) Clean about two cm around the point where the needle will go in.
i) Insert the needle at an angle of 90° to the skin surface and depress the plunger slowly and steadily.

SC injection
h) Clean about two cm around the point where the needle will go in.
i) Insert the needle at the base of the pinched-up skin at an angle of 45° to the skin surface and depress the plunger slowly and steadily.

N.V. Organon Oss Holland