ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

   Puregon®

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   Puregon® 50 I.U. consists of a freeze-dried powder and a solvent for reconstitution. The powder for injection contains the active ingredient recombinant follicle-stimulating hormone (FSH) (follitropin beta).

   One container of Puregon® 50 I.U. contains 50 I.U. FSH activity corresponding to 5 microgram of protein (specific in vivo bioactivity equal to approximately 10 000 I.U. FSH / mg protein⁷).

   Puregon® 50 I.U. is in the form of a lyophilised sphere or lyosphere.

3. **PHARMACEUTICAL FORM**

   Powder for injection. Prior to use, Puregon® is reconstituted with the solvent for parenteral use provided.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic 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)].

4.2 **Posology and method of 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.

   **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 oestradiol levels.

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⁷ as determined by the Ph.Eur. test for FSH in vivo bioactivity and on the basis of the molar extinction coefficient at 277 nm (εₘ; mg⁻¹ cm⁻¹) = 1.066.
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 in general the treatment success rate remains stable during the first four 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 oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol 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 oestradiol 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 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 150-225 I.U. 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 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 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 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. In order to avoid injection of large volumes 3 to 4 lyospheres of Puregon® may be dissolved in 1 ml of solvent. When only 1 or 2 lyospheres are required the volume may be reduced to 0.5 ml. After reconstitution of each sphere, it should be checked visually whether all freeze-dried material has dissolved completely. The reconstituted solution should not be used if it contains particles or is not clear.

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.
4.3 **Contraindications**
- Tumours of the 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.

4.4 **Special warnings and special precautions for use**
- 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 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. 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.

4.5 **Interaction with other medications 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.

4.6 **Pregnancy and lactation**
Puregon® must not be used during pregnancy and lactation.

4.7 **Effects on ability to drive and use machines**
As far as known this medicine has no influence on alertness and concentration.
4.8 Undesirable effects
Undesirable effects
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’ Section 4.4).
Clinical use of Puregon® by the i.m. or s.c. 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 pregnancies has been seen. In rare instances, arterio-thromboembolisms have been associated with menotrophin/human chorionic gonadotrophin therapy. This may also occur with Puregon®/hCG therapy.

4.9 Overdose
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, Section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties (atc classification: gonadotrophins, go3g)
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.

5.2 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, 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.

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 or in the in vitro chromosome aberration test with human lymphocytes.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
The powder for injection contains sucrose, sodium citrate, and polysorbate 20. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid. The ampoule of solvent contains sodium chloride (4.5mg) and water for injections (1.0ml). The quality of all excipients is in accordance with the specifications of the European Pharmacopoeia (Ph.Eur.).

6.2 Incompatibilities
Incompatibilities with other medication have not been investigated and mixing with other medication should therefore be avoided.

6.3 Shelf-life
The shelf-life of Puregon® is two years under the conditions specified in section 6.4. Puregon® may be used until the expiration date indicated on the package.

6.4 Special precautions for storage
Store below 30°C. Protect from light. Do not freeze. Store Puregon® out of reach of children.

6.5 Nature and contents of containers
Boxes of Puregon® 50 I.U. contain:
- 1 ampoule of follitropin beta plus 1 ampoule solvent or
- 3 ampoules of follitropin beta plus 3 ampoules solvent or
- 5 ampoules of follitropin beta plus 5 ampoules solvent or
- 10 ampoules of follitropin beta plus 10 ampoules solvent.
Ampoules of Puregon® 50 I.U. contain a sterile lyophilised sphere (called lyosphere) corresponding to 50 I.U. FSH activity.
Ampoules solvent contain 1 ml saline 0.45%.

6.6 Instructions for use/handling
Puregon® should be reconstituted with the solvent provided using a gentle, swirling motion. Vigorous shaking should be avoided. Do not use if the solution contains particles or if the solution is not clear. When dissolving more than one sphere, it should be checked visually whether all freeze-dried material has dissolved completely before the solution is transferred to the next ampoule to be reconstituted. Since an opened ampoule cannot be resealed in such a way to further guarantee the sterility of the contents, the solution should be used immediately after reconstitution. Disgard any remaining solution after single use.

7. MARKETING AUTHORISATION HOLDER
N.V. Organon, P.O.Box 20, 5340 BH Oss, The Netherlands.

8. MARKETING AUTHORISATION NUMBER
EU/1/96/008/001 1 ampoule
EU/1/96/008/002 3 ampoules
EU/1/96/008/003 5 ampoules
EU/1/96/008/004 10 ampoules

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION
May 3rd 1996.
10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

   Puregon®

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   Puregon® 75 I.U. consists of a freeze-dried powder and a solvent for reconstitution. The powder for injection contains the active ingredient recombinant follicle-stimulating hormone (FSH) (follitropin beta).

   One container of Puregon® 75 I.U. contains 75 I.U. FSH activity corresponding to 7,5 microgram of protein (specific in vivo bioactivity equal to approximately 10 000 I.U. FSH / mg protein\(^8\)).

   Puregon® 75 I.U. is in the form of a lyophilised cake.

3. **PHARMACEUTICAL FORM**

   Powder for injection. Prior to use, Puregon® is reconstituted with the solvent for parenteral use provided.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic 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)].

4.2 **Posology and method of 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.

   **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 oestradiol levels.

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\(^1\) as determined by the Ph.Eur. test for FSH in vivo bioactivity and on the basis of the molar extinction coefficient at 277 nm \((\epsilon_s \text{, mg}^{-1}\text{cm}^{-1}) = 1.066\).
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 in general the treatment success rate remains stable during the first four 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 oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol 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 oestradiol 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 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 150-225 I.U. 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 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 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 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. In order to avoid injection of large volumes 3 to 4 cakes of Puregon® may be dissolved in 1 ml of solvent. When only 1 or 2 cakes are required the volume may be reduced to 0.5 ml. After reconstitution of each cake, it should be checked visually whether all freeze-dried material has dissolved completely. The reconstituted solution should not be used if it contains particles or is not clear.

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.

### 4.3 Contraindications
• Tumours of the 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.

4.4 Special warnings and special precautions for use
• 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 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. 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.

4.5 Interaction with other medicaments 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.

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

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

4.8 Undesirable effects
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’ Section 4.4).

Clinical use of Puregon® by the i.m. or s.c. 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 pregnancies has been seen. In rare instances, arterio-thromboembolisms have been associated with menotrophin/human chorionic gonadotrophin therapy. This may also occur with Puregon®/hCG therapy.

4.9 Overdose
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, Section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties (ATC classification: gonadotrophins, go3g)
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 intrafallopian 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.

5.2 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, 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.

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 or in the in vitro chromosome aberration test with human lymphocytes.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
The powder for injection contains sucrose, sodium citrate, and polysorbate 20. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid. The ampoule of solvent contains sodium chloride (4.5mg) and water for injections (1.0ml). The quality of all excipients is in accordance with the specifications of the European Pharmacopoeia (Ph.Eur.).

6.2 Incompatibilities
Incompatibilities with other medication have not been investigated and mixing with other medication should therefore be avoided.

6.3 Shelf-life
The shelf-life of Puregon® is two years under the conditions specified in section 6.4 Puregon® may be used until the expiration date indicated on the package.

6.4 Special precautions for storage
Store below 30°C. Protect from light. Do not freeze. Store Puregon® out of reach of children

6.5 Nature and contents of containers
Boxes of Puregon® 75 I.U. contain:
· 1 vial of follitropin beta plus 1 ampoule solvent or
· 3 vials of follitropin beta plus 3 ampoules solvent or
· 5 vials of follitropin beta plus 5 ampoules solvent or
· 10 vials of follitropin beta plus 10 ampoules solvent.
Vials of Puregon® 75 I.U. contain a sterile lyophilised cake corresponding to 75 I.U. FSH activity. Ampoules solvent contain 1 ml saline 0.45%.

6.6 Instructions for use/handling
Puregon® should be reconstituted with the solvent provided using a gentle, swirling motion. Vigorous shaking should be avoided. Do not use if the solution contains particles or if the solution is not clear. When dissolving more than one cake, it should be checked visually whether all freeze-dried material has dissolved completely before the solution is transferred to the next vial to be reconstituted. The content of a vial should also be used immediately after reconstitution. Disgard any remaining solution after single use.

7. MARKETING AUTHORISATION HOLDER
N.V. Organon, P.O.Box 20, 5340 BH Oss, The Netherlands.

8. MARKETING AUTHORISATION NUMBER
EU/1/96/008/005 1 vial
EU/1/96/008/006 3 vials
EU/1/96/008/007 5 vials
EU/1/96/008/008 10 vials

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

Puregon®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Puregon® 100 I.U. consists of a freeze-dried powder and a solvent for reconstitution. The powder for injection contains the active ingredient recombinant follicle-stimulating hormone (FSH) (follitropin beta).

One container of Puregon® 100 I.U. contains 100 I.U. FSH activity corresponding to 10 microgram of protein (specific in vivo bioactivity equal to approximately 10 000 I.U. FSH / mg protein9).

Puregon® 100 I.U. is in the form of a lyophilised sphere or lyosphere.

3. PHARMACEUTICAL FORM

Powder for injection. Prior to use, Puregon® is reconstituted with the solvent for parenteral use provided.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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)].

4.2 Posology and method of 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.

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 oestradiol levels.

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9 as determined by the Ph.Eur. test for FSH in vivo bioactivity and on the basis of the molar extinction coefficient at 277 nm (\( \epsilon_s ; \text{mg}^{-1}\text{cm}^{-1} \) ) = 1.066.
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 in general the treatment success rate remains stable during the first four 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 oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol 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 oestradiol 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 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 150-225 I.U. 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 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 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 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. In order to avoid injection of large volumes 3 to 4 lyospheres of Puregon® may be dissolved in 1 ml of solvent. When only 1 or 2 lyospheres are required the volume may be reduced to 0.5 ml. After reconstitution of each sphere, it should be checked visually whether all freeze-dried material has dissolved completely. The reconstituted solution should not be used if it contains particles or is not clear.

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.
4.3 **Contraindications**
- Tumours of the 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.

4.4 **Special warnings and special precautions for use**
- 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 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. 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.

4.5 **Interaction with other medicaments 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.

4.6 **Pregnancy and lactation**
Puregon® must not be used during pregnancy and lactation.

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

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’ Section 4.4). Clinical use of Puregon® by the i.m. or s.c. 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 pregnancies has been seen. In rare instances, arterio-thromboembolisms have been associated with menotrophin/human chorionic gonadotrophin therapy. This may also occur with Puregon®/hCG therapy.

4.9 Overdose

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, Section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties (atc classification: gonadotrophins, go3g)

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 intratubal 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.

5.2 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, 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.

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 or in the in vitro chromosome aberration test with human lymphocytes.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
The powder for injection contains sucrose, sodium citrate, and polysorbate 20. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid. The ampoule of solvent contains sodium chloride (4.5mg) and water for injections (1.0ml). The quality of all excipients is in accordance with the specifications of the European Pharmacopoeia (Ph.Eur.).

6.2 Incompatibilities
Incompatibilities with other medication have not been investigated and mixing with other medication should therefore be avoided.

6.3 Shelf-life
The shelf-life of Puregon® is two years under the conditions specified in section 6.4. Puregon® may be used until the expiration date indicated on the package.

6.4 Special precautions for storage
Store below 30°C. Protect from light. Do not freeze. Store Puregon® out of reach of children.

6.5 Nature and contents of containers
Boxes of Puregon® 100 I.U. contain:
- 1 ampoule of follitropin beta plus 1 ampoule solvent or
- 3 ampoules of follitropin beta plus 3 ampoules solvent or
- 5 ampoules of follitropin beta plus 5 ampoules solvent or
- 10 ampoules of follitropin beta plus 10 ampoules solvent.
Ampoules of Puregon® 100 I.U. contain a sterile lyophilised sphere (called lyosphere) corresponding to 100 I.U. FSH activity.
Ampoules solvent contain 1 ml saline 0.45%.

6.6 Instructions for use/handling
Puregon® should be reconstituted with the solvent provided using a gentle, swirling motion. Vigorous shaking should be avoided. Do not use if the solution contains particles or if the solution is not clear. When dissolving more than one sphere, it should be checked visually whether all freeze-dried material has dissolved completely before the solution is transferred to the next ampoule to be reconstituted. Since an opened ampoule cannot be resealed in such a way to further guarantee the sterility of the contents, the solution should be used immediately after reconstitution. Disgard any remaining solution after single use.

7. MARKETING AUTHORISATION HOLDER
N.V. Organon, P.O.Box 20, 5340 BH Oss, The Netherlands.

8. MARKETING AUTHORISATION NUMBER
EU/1/96/008/009 1 ampoule
EU/1/96/008/010 3 ampoules
EU/1/96/008/011 5 ampoules
EU/1/96/008/012 10 ampoules

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION
May 3rd 1996

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

Puregon®

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Puregon® 150 I.U. consists of a freeze-dried powder and a solvent for reconstitution. The powder for injection contains the active ingredient recombinant follicle-stimulating hormone (FSH) (follitropin beta).

One container of Puregon® 150 I.U. contains 150 I.U. FSH activity corresponding to 15 microgram of protein (specific in vivo bioactivity equal to approximately 10 000 I.U. FSH / mg protein\(^{10}\)).

Puregon® 150 I.U. is in the form of a lyophilised sphere or lyosphere.

3. **PHARMACEUTICAL FORM**

Powder for injection. Prior to use, Puregon® is reconstituted with the solvent for parenteral use provided.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic 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)].

4.2 **Posology and method of 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.

**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 oestradiol levels.

\(^{10}\) as determined by the Ph.Eur. test for FSH in vivo bioactivity and on the basis of the molar extinction coefficient at 277 nm \((\varepsilon_s ; \text{mg}^{-1} \text{cm}^{-1}) = 1.066\).
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 in general the treatment success rate remains stable during the first four 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 oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol 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 oestradiol 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 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 150-225 I.U. 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 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 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 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. In order to avoid injection of large volumes 3 to 4 lyospheres of Puregon® may be dissolved in 1 ml of solvent. When only 1 or 2 lyospheres are required the volume may be reduced to 0.5 ml. After reconstitution of each sphere, it should be checked visually whether all freeze-dried material has dissolved completely. The reconstituted solution should not be used if it contains particles or is not clear.

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.
4.3 **Contraindications**
- Tumours of the 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.

4.4 **Special warnings and special precautions for use**
- 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 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. 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.

4.5 **Interaction with other medicaments 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.

4.6 **Pregnancy and lactation**
Puregon® must not be used during pregnancy and lactation.

4.7 **Effects on ability to drive and use machines**
As far as known this medicine has no influence on alertness and concentration.
4.8 Undesirable effects
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’ Section 4.4).
Clinical use of Puregon® by the i.m. or s.c. 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 pregnancies has been seen. In rare instances, arterio-thromboembolisms have been associated with menotrophin/human chorionic gonadotrophin therapy. This may also occur with Puregon®/hCG therapy.

4.9 Overdose
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, Section 4.4)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties (atc classification: gonadotrophins, go3g)
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.

5.2 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, 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.

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 or in the in vitro chromosome aberration test with human lymphocytes.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
The powder for injection contains sucrose, sodium citrate, and polysorbate 20. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid. The ampoule of solvent contains sodium chloride (4.5mg) and water for injections (1.0ml). The quality of all excipients is in accordance with the specifications of the European Pharmacopoeia (Ph.Eur.)

6.2 Incompatibilities
Incompatibilities with other medication have not been investigated and mixing with other medication should therefore be avoided.

6.3 Shelf-life
The shelf-life of Puregon® is two years under the conditions specified in section 6.4 Puregon® may be used until the expiration date indicated on the package.

6.4 Special precautions for storage
Store below 30°C. Protect from light. Do not freeze.
Store Puregon® out of reach of children

6.5 Nature and contents of containers
Boxes of Puregon® 150 I.U. contain:
- 1 ampoule of follitropin beta plus 1 ampoule solvent or
- 3 ampoules of follitropin beta plus 3 ampoules solvent or
- 5 ampoules of follitropin beta plus 5 ampoules solvent or
- 10 ampoules of follitropin beta plus 10 ampoules solvent.
Ampoules of Puregon® 150 I.U. contain a sterile lyophilised sphere (called lyosphere) corresponding to 150 I.U. FSH activity.
Ampoules solvent contain 1 ml saline 0.45%.

6.6 Instructions for use/handling
Puregon® should be reconstituted with the solvent provided using a gentle, swirling motion. Vigorous shaking should be avoided. Do not use if the solution contains particles or if the solution is not clear. When dissolving more than one sphere, it should be checked visually whether all freeze-dried material has dissolved completely before the solution is transferred to the next ampoule to be reconstituted. Since an opened ampoule cannot be resealed in such a way to further guarantee the sterility of the contents, the solution should be used immediately after reconstitution. Discard any remaining solution after single use.

7. MARKETING AUTHORISATION HOLDER
N.V. Organon, P.O.Box 20, 5340 BH Oss, The Netherlands.

8. MARKETING AUTHORISATION NUMBER
EU/1/96/008/013 1 ampoule
EU/1/96/008/014 3 ampoules
EU/1/96/008/015 5 ampoules
EU/1/96/008/016 10 ampoules

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION
May 3rd 1996

10. DATE OF REVISION OF THE TEXT
ANNEX III
LABELLING AND PACKAGE LEAFLET
B. PACKAGE LEAFLET
WHAT YOU SHOULD KNOW ABOUT PUREGON®

Please read the following information carefully before using this medicine. The leaflet contains details about Puregon®, as well as some general advice on using medicines. If you have any questions or other concerns, please ask your doctor or pharmacist.

NAME OF YOUR MEDICINE
The medicine prescribed for you is called Puregon®.

COMPOSITION AND STRENGTH - what your medicine contains
Puregon® 50 I.U. contains a hormone known as follicle-stimulating hormone (or FSH) in a strength of 50 I.U. per ampoule.
Besides FSH, the powder contains sucrose, sodium citrate, and polysorbate 20; the solvent contains sodium chloride (4.5mg) and water for injections (1.0ml).

PHARMACEUTICAL FORM - what your medicine consists of
Puregon® 50 I.U. is supplied in a glass ampoule as a dry powder, which should be dissolved with the solvent contained in a second glass ampoule. It is available in packs of 1, 3, 5 and 10 ampoules.

THERAPEUTIC GROUP - how your medicine works
Gonadotropins (including FSH) play an important role in human fertility and reproduction. FSH is needed in women for the growth and development of follicles in the ovaries. Follicles are small round sacs that contain the egg cells.

MARKETING AUTHORISATION HOLDER
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands

MANUFACTURERS
Organon (Ireland) Ltd, P.O. Box 2857, Swords, Co. Dublin, Ireland
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands
Organon Laboratories Ltd, Newhouse, Lanarkshire, ML1 5SH, Scotland

INDICATIONS - when your medicine is used
Puregon® is used to treat infertility in either of the following situations:
- In women who are not ovulating, Puregon® can be used to cause ovulation in women who have not responded to treatment with clomiphene citrate.
- In women undergoing assisted reproduction techniques (ART), including in-vitro fertilisation (IVF) and other methods, Puregon® can be used to bring about the development of multiple follicles.

CONTRAINDICATIONS - when you should not use this medicine
There are certain medical conditions in which Puregon® should not be used. Do not use Puregon® if you:
- have a tumour of the ovary, breast, uterus, pituitary gland or hypothalamus.
- are pregnant or breast-feeding.
- are allergic to any of the substances of Puregon®.
- have heavy or irregular vaginal bleeding where the cause is not known.
- have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD).

This medicine should not be used when a condition exists which makes a normal pregnancy impossible. This may occur with primary ovarian failure, when there are fibroids in the uterus or when certain malformations of the sexual organs are present.
SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Caution
Close supervision of patients by a doctor is very important. Usually ultrasound scans of the ovaries are regularly made, and blood or urine samples are regularly taken. The results of these tests allow the doctor to choose the correct dose of Puregon® from day to day. This is very important since too high a dose of FSH may lead to rare but serious complications in which the ovaries become overstimulated. This may be noticed as pain in the abdomen. Regular monitoring of the response to FSH-treatment helps the doctor to prevent ovarian overstimulation. So contact your doctor without delay if you are experiencing significant abdominal pain, also if this occurs some days after the last injection has been given.

INTERACTIONS - when you are taking other medicines
If Puregon® is used in combination with clomiphene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Puregon® may be needed to achieve a response.

PREGNANCY AND LACTATION - When you are pregnant or breast-feeding
You should not be given Puregon® if you are already pregnant, or suspect that you might be pregnant, or if you are breast-feeding.
In pregnancies occurring after treatment with gonadotropic preparations, there is an increased risk of having twins or multiplets. There is a slightly increased risk of ectopic pregnancy in women with damaged fallopian tubes.
In women undergoing fertility treatment, there is a slightly higher risk of miscarriage.

ABILITY TO DRIVE OR OPERATE MACHINERY
As far as is known, Puregon® has no effect on alertness and concentration.

DOSAGE - the amount of medicine given
Your doctor will decide on the dose of Puregon® to be given. Usually treatment starts with 75 to 225 I.U. FSH each day. This dose may be increased as your treatment progresses. Further details of 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, follicle growth is checked by means of ultrasound scanning and measurement of the amount of estradiol (female sex hormone) in blood or urine. The dosage recommendations given below are in line with those usually applied for urinary FSH.

- Women who are not ovulating
  Treatment usually starts with the administration of 75 I.U. FSH per day. The starting 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 estradiol levels indicate an adequate response. The daily dose is then maintained until a follicle of adequate size is present. Usually 7 to 14 days of treatment are sufficient. The administration of Puregon® is then stopped and ovulation can be induced by administering human chorionic gonadotropin (hCG).

- Medically assisted reproduction programs e.g. IVF
  A starting dose of 150-225 I.U. is recommended for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their 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.
  When a sufficient number of follicles of adequate size are present, the final phase of maturation of the follicles is induced by administration of hCG. Oocyte (egg) retrieval is performed 34-35 hours later.

METHOD AND ROUTE OF ADMINISTRATION - how injections are given
Puregon® only works if it is injected in a muscle or under the skin.
The very first injection of Puregon® should only be given under medical supervision.
The dry powder should be dissolved with the solvent contained in the ampoule with fluid and this solution should be administered immediately. To avoid injection of large volumes, 3 to 4 lyospheres of Puregon may be dissolved in 1 ml of solvent. When only 1 or 2 lyospheres are required, the volume may be reduced to 0.5 ml. The injections are given slowly into a muscle (for instance in the buttock, upper leg or upper arm) or just under the skin (in the abdominal wall, for example). Injections into a muscle should only be given by a doctor or a nurse. Subcutaneous injections may, in some cases, be given by you or your partner. Your doctor will tell you when and how to do this.

If you administer Puregon® to yourself, follow the instructions below carefully and Puregon® will be administered properly and with minimal discomfort.

**Step 1 - Preparing Puregon®**

Puregon® comes in two glass ampoules whose contents must be mixed together. First, break the top off the ampoule with the sodium chloride solution (a, b). Draw up the liquid through the needle into the syringe (c). Break open the second ampoule containing the freeze-dried sphere (with the black dot in the position as indicated in the figures a and b) and add the sodium chloride solution from the syringe (d). DO NOT SHAKE, but gently swirl until the solution is clear. Generally the Puregon® dissolves immediately. Should the solution contain particles or not become clear, do not use.

If you need to dissolve more than one freeze-dried sphere, then repeat the actions described under points c and d until the required number of freeze-dried spheres is dissolved. Please make sure that all handling is performed in such a way that sterile conditions are maintained during the dissolution procedure (e.g. do not put the syringe down without covering the needle with the protective cap).

Draw the Puregon® solution up into the empty syringe (e), and now replace the needle with a sterile injection needle (f). 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 (g).

**Step 2 - The injection site**

**Intramuscular injection**

The best site for intramuscular injection of Puregon® is the buttock muscle. The area indicated in the diagram (the upper, outer quadrant) contains a large volume of muscle with few blood vessels or major nerves. Stretching the skin helps the needle to go in more easily and pushes the tissue beneath the skin out of the way. This helps the solution to disperse correctly.

**Subcutaneous injection**

The best site for subcutaneous injection is in the abdomen around the navel where there is a lot of loose skin and layers of fatty tissue. Pinch up a large area of skin between the finger and thumb. 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**
**Intramuscular:** The needle should be inserted right up to the hilt at an angle of 90° to the skin surface. Pushing in with a quick thrust causes least discomfort.

**Subcutaneous:** The needle should be inserted at the base of the pinched-up skin at an angle of 45° to the skin surface.

![IM IM SC SC]

**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 new ampoules of Puregon® and sodium chloride solution.

**Step 6 - Injecting the solution**
Depress the plunger **slowly** and steadily, so the solution is correctly injected and the muscle or 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.
Any remaining solution should be discarded.
Do not mix Puregon® solution with any other medicines.

**OVERDOSE**
Too high a dose may cause overstimulation of the ovaries. See Section on Undesirable Effects below.

**UNDESIRABLE EFFECTS - unwanted effects**
A serious complication with FSH is unwanted overstimulation of the ovaries. This condition is rare, and the risk can be reduced by careful monitoring of follicle development during treatment. The first symptoms of ovarian overstimulation may be noticed as pain in the abdomen, feeling sick or diarrhoea. In more severe cases symptoms may include enlargement of the ovaries, accumulation of fluid in the abdomen and/or chest, weight gain and the occurrence of blood clots in the circulation. Contact your doctor without delay if you are experiencing any of these symptoms, also if they develop some days after the last injection has been given.
Minor side effects include bruising, pain, redness, swelling and itching at the site of the injection.

**SHELF LIFE AND STORAGE PRECAUTIONS - looking after your medicine**
Keep Puregon® in the original box in a safe place out of the reach of children.
Puregon should be stored below 30°C and protected from light. Do not freeze.
The expiry date is printed on the box after 'Use by:' and on the label after 'Exp.'. Do not use Puregon® after this date.
Any unused solution should be discarded.
This information was last updated in

**GENERAL THINGS TO REMEMBER ABOUT MEDICINES**
1. This medicine has been prescribed only for your current medical problem. It should not be used for other medical conditions.
2. Never give your medicine to anyone else and do not use medicines meant for other people.
3. Tell your doctor treating you which medicines you are currently taking. Always carry a medical information card stating which medicines you are using. This can be very important in case you are involved in an accident.
4. Return unused medicines to the pharmacy for disposal.
5. Make sure that the people you live with or who look after you read this information
WHAT YOU SHOULD KNOW ABOUT PUREGON®

Please read the following information carefully before using this medicine. The leaflet contains details about Puregon®, as well as some general advice on using medicines. If you have any questions or other concerns, please ask your doctor or pharmacist.

NAME OF YOUR MEDICINE
The medicine prescribed for you is called Puregon®

COMPOSITION AND STRENGTH - what your medicine contains
Puregon® 75 I.U. contains a hormone known as follicle-stimulating hormone (or FSH) in a strength of 75 I.U. per vial. Besides FSH, the powder contains sucrose, sodium citrate, and polysorbate 20; the solvent contains sodium chloride (4.5mg) and water for injections (1.0ml).

PHARMACEUTICAL FORM - what your medicine consists of
Puregon® 75 I.U. is supplied in a glass vial as a dry powder, which should be dissolved with the solvent contained in a second glass ampoule. It is available in packs of 1, 3, 5 and 10 vials.

THERAPEUTIC GROUP - how your medicine works
Gonadotropins (including FSH) play an important role in human fertility and reproduction. FSH is needed in women for the growth and development of follicles in the ovaries. Follicles are small round sacs that contain the egg cells.

MARKETING AUTHORISATION HOLDER:
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands

MANUFACTURER
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands

INDICATIONS - when your medicine is used
Puregon® is used to treat infertility in either of the following situations:
- In women who are not ovulating, Puregon® can be used to cause ovulation in women who have not responded to treatment with clomiphene citrate.
- In women undergoing assisted reproduction techniques (ART), including in-vitro fertilisation (IVF) and other methods, Puregon® can be used to bring about the development of multiple follicles.

CONTRAINDICATIONS - when you should not use this medicine
There are certain medical conditions in which Puregon® should not be used. Do not use Puregon® if you:
- have a tumour of the ovary, breast, uterus, pituitary gland or hypothalamus.
- are preganant or breast-feeding.
- are allergic to any of the substances of Puregon®.
- have heavy or irregular vaginal bleeding where the cause is not known.
- have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD).

This medicine should not be used when a condition exists which makes a normal pregnancy impossible. This may occur with primary ovarian failure, when there are fibroids in the uterus or when certain malformations of the sexual organs are present.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Caution
Close supervision of patients by a doctor is very important. Usually ultrasound scans of the ovaries
are regularly made, and blood or urine samples are regularly taken. The results of these tests allow the doctor to choose the correct dose of Puregon® from day to day. This is very important since too high a dose of FSH may lead to rare but serious complications in which the ovaries become overstimulated. This may be noticed as pain in the abdomen. Regular monitoring of the response to FSH-treatment helps the doctor to prevent ovarian overstimulation. So contact your doctor without delay if you are experiencing significant abdominal pain, also if this occurs some days after the last injection has been given.

INTERACTIONS - when you are taking other medicines
If Puregon® is used in combination with clomiphene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Puregon® may be needed to achieve a response.

PREGNANCY AND LACTATION - When you are pregnant or breast-feeding
You should not be given Puregon® if you are already pregnant, or suspect that you might be pregnant, or if you are breast-feeding. In pregnancies occurring after treatment with gonadotropic preparations, there is an increased risk of having twins or multiples. There is a slightly increased risk of ectopic pregnancy in women with damaged fallopian tubes. In women undergoing fertility treatment, there is a slightly higher risk of miscarriage.

ABILITY TO DRIVE OR OPERATE MACHINERY
As far as is known, Puregon® has no effect on alertness and concentration.

DOSAGE - the amount of medicine given
Your doctor will decide on the dose of Puregon® to be given. Usually treatment starts with 75 to 225 I.U. FSH each day. This dose may be increased as your treatment progresses. Further details of 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, follicle growth is checked by means of ultrasound scanning and measurement of the amount of estradiol (female sex hormone) in blood or urine. The dosage recommendations given below are in line with those usually applied for urinary FSH.

- **Women who are not ovulating**
  Treatment usually starts with the administration of 75 I.U. FSH per day. The starting 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 estradiol levels indicate an adequate response. The daily dose is then maintained until a follicle of adequate size is present. Usually 7 to 14 days of treatment are sufficient. The administration of Puregon® is then stopped and ovulation can be induced by administering human chorionic gonadotropin (hCG).

- **Medically assisted reproduction programs e.g. IVF**
  A starting dose of 150-225 I.U. is recommended for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their 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.
  When a sufficient number of follicles of adequate size are present, the final phase of maturation of the follicles is induced by administration of hCG. Oocyte (egg) retrieval is performed 34-35 hours later.

METHOD AND ROUTE OF ADMINISTRATION - how injections are given
Puregon® only works if it is injected in a muscle or under the skin.
The very first injection of Puregon® should only be given under medical supervision.
The dry powder should be dissolved with the solvent contained in the ampoule with fluid and this solution should be administered immediately.
To avoid injection of large volumes 3 to 4 cakes of Puregon may be dissolved in 1 ml of solvent. When only 1 or 2 cakes are required the volume may be reduced to 0.5 ml.
The injections are given slowly into a muscle (for instance in the buttock, upper leg or upper arm) or just under the skin (in the abdominal wall, for example). Injections into a muscle should only be given by a doctor or a nurse. Subcutaneous injections may, in some cases, be given by you or your partner. Your doctor will tell you when and how to do this.

If you administer Puregon® to yourself, follow the instructions below carefully and Puregon® will be administered properly and with minimal discomfort.
Step 1 - Preparing Puregon®

Puregon® comes in a glass vial whose content must be mixed together with the solvent in the glass ampoule. First, break the top off the ampoule with the sodium chloride solution (a, b). Draw up the liquid through the needle into the syringe (c). Remove the white flip-off cap of the vial of Puregon® and inject the sodium chloride solution from the syringe through the rubber closure into the vial containing the freeze-dried cake. (d.) DO NOT SHAKE, but gently swirl until the solution is clear. Generally the Puregon® dissolves immediately. Should the solution contain particles or not become clear, do not use. If you need to dissolve more than one freeze-dried cake, then repeat the actions described under points c and d until the required number of freeze-dried cakes is dissolved. Please make sure that all handling is performed in such a way that sterile conditions are maintained during the dissolution procedure (e.g. do not put the syringe down without covering the needle with the protective cap).

Draw the Puregon® solution up into the empty syringe, (e) and now replace the needle with a sterile injection needle. (f.) 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. (g).

Step 2 - The injection site

Intramuscular injection

The best site for intramuscular injection of Puregon® is the buttock muscle. The area indicated in the diagram (the upper, outer quadrant) contains a large volume of muscle with few blood vessels or major nerves. Stretching the skin helps the needle to go in more easily and pushes the tissue beneath the skin out of the way. This helps the solution to disperse correctly.

Subcutaneous injection

The best site for subcutaneous injection is in the abdomen around the navel where there is a lot of loose skin and layers of fatty tissue. Pinch up a large area of skin between the finger and thumb. 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

Intramuscular: The needle should be inserted right up to the hilt at an angle of 90° to the skin surface. Pushing in with a quick thrust causes least discomfort.

Subcutaneous: The needle should be inserted at the base of the pinched-up skin at an angle of 45° to the skin surface.

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 new ampoules of Puregon® and sodium chloride solution.

**Step 6 - Injecting the solution**
Depress the plunger slowly and steadily, so the solution is correctly injected and the muscle or 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.

Any remaining solution should be discarded.

Do not mix Puregon® solution with any other medicines.

**OVERDOSE**
Too high a dose may cause overstimulation of the ovaries. See Section on Undesirable Effects below.

**UNDISIRABLE EFFECTS - unwanted effects**
A serious complication with FSH is unwanted overstimulation of the ovaries. This condition is rare, and the risk can be reduced by careful monitoring of follicle development during treatment. The first symptoms of ovarian overstimulation may be noticed as pain in the abdomen, feeling sick or diarrhoea. In more severe cases symptoms may include enlargement of the ovaries, accumulation of fluid in the abdomen and/or chest, weight gain and the occurrence of blood clots in the circulation.

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

Minor side effects include bruising, pain, redness, swelling and itching at the site of the injection.

**SHELF LIFE AND STORAGE PRECAUTIONS - looking after your medicine**
Keep Puregon® in the original box in a safe place out of the reach of children.

Puregon should be stored below 30°C and protected from light. Do not freeze.

The expiry date is printed on the box after ‘Use by: ’ and on the label after ‘Exp.’. Do not use Puregon® after this date.

Any unused solution should be discarded.

This information was last updated in

**GENERAL THINGS TO REMEMBER ABOUT MEDICINES**
1. This medicine has been prescribed only for your current medical problem. It should not be used for other medical conditions.
2. Never give your medicine to anyone else and do not use medicines meant for other people.
3. Tell your doctor treating you which medicines you are currently taking. Always carry a medical information card stating which medicines you are using. This can be very important in case you are involved in an accident.
4. Return unused medicines to the pharmacy for disposal.
5. Make sure that the people you live with or who look after you read this information.
WHAT YOU SHOULD KNOW ABOUT PUREGON®

Please read the following information carefully before using this medicine. The leaflet contains details about Puregon®, as well as some general advice on using medicines. If you have any questions or other concerns, please ask your doctor or pharmacist.

NAME OF YOUR MEDICINE
The medicine prescribed for you is called Puregon®.

COMPOSITION AND STRENGTH - what your medicine contains
Puregon®100 I.U. contains a hormone known as follicle-stimulating hormone (or FSH) in a strength of 100 I.U. per ampoule. Besides FSH, the powder contains sucrose, sodium citrate, and polysorbate 20; the solvent contains sodium chloride (4.5mg) and water for injections (1.0ml).

PHARMACEUTICAL FORM - what your medicine consists of
Puregon® 100 I.U. is supplied in a glass ampoule as a dry powder, which should be dissolved with the solvent contained in a second glass ampoule. It is available in packs of 1, 3, 5 and 10 ampoules.

THERAPEUTIC GROUP - how your medicine works
Gonadotropins (including FSH) play an important role in human fertility and reproduction. FSH is needed in women for the growth and development of follicles in the ovaries. Follicles are small round sacs that contain the egg cells.

MARKETING AUTHORISATION HOLDER
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands

MANUFACTURERS
Organon (Ireland) Ltd, P.O. Box 2857, Swords, Co. Dublin, Ireland
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands
Organon Laboratories Ltd, Newhouse, Lanarkshire, ML1 5SH, Scotland

INDICATIONS - when your medicine is used
Puregon® is used to treat infertility in either of the following situations:
- In women who are not ovulating, Puregon® can be used to cause ovulation in women who have not responded to treatment with clomiphene citrate.
- In women undergoing assisted reproduction techniques (ART), including in-vitro fertilisation (IVF) and other methods, Puregon® can be used to bring about the development of multiple follicles.

CONTRAINDICATIONS - when you should not use this medicine
There are certain medical conditions in which Puregon® should not be used. Do not use Puregon® if you:
- have a tumour of the ovary, breast, uterus, pituitary gland or hypothalamus.
- are pregnant or breast-feeding.
- are allergic to any of the substances of Puregon®.
- have heavy or irregular vaginal bleeding where the cause is not known.
- have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD).

This medicine should not be used when a condition exists which makes a normal pregnancy impossible. This may occur with primary ovarian failure, when there are fibroids in the uterus or when certain malformations of the sexual organs are present.
SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Caution
Close supervision of patients by a doctor is very important. Usually ultrasound scans of the ovaries are regularly made, and blood or urine samples are regularly taken. The results of these tests allow the doctor to choose the correct dose of Puregon® from day to day. This is very important since too high a dose of FSH may lead to rare but serious complications in which the ovaries become overstimulated. This may be noticed as pain in the abdomen. Regular monitoring of the response to FSH-treatment helps the doctor to prevent ovarian overstimulation. So contact your doctor without delay if you are experiencing significant abdominal pain, also if this occurs some days after the last injection has been given.

INTERACTIONS - when you are taking other medicines
If Puregon® is used in combination with clomiphene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Puregon® may be needed to achieve a response.

PREGNANCY AND LACTATION - When you are pregnant or breast-feeding
You should not be given Puregon® if you are already pregnant, or suspect that you might be pregnant, or if you are breast-feeding.
In pregnancies occurring after treatment with gonadotropic preparations, there is an increased risk of having twins or multiplets. There is a slightly increased risk of ectopic pregnancy in women with damaged fallopian tubes.
In women undergoing fertility treatment, there is a slightly higher risk of miscarriage.

ABILITY TO DRIVE OR OPERATE MACHINERY
As far as is known, Puregon® has no effect on alertness and concentration.

DOSAGE - the amount of medicine given
Your doctor will decide on the dose of Puregon® to be given. Usually treatment starts with 75 to 225 I.U. FSH each day. This dose may be increased as your treatment progresses. Further details of 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, follicle growth is checked by means of ultrasound scanning and measurement of the amount of estradiol (female sex hormone) in blood or urine. The dosage recommendations given below are in line with those usually applied for urinary FSH.

• Women who are not ovulating
  Treatment usually starts with the administration of 75 I.U. FSH per day. The starting 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 estradiol levels indicate an adequate response. The daily dose is then maintained until a follicle of adequate size is present. Usually 7 to 14 days of treatment are sufficient. The administration of Puregon® is then stopped and ovulation can be induced by administering human chorionic gonadotropin (hCG).

• Medically assisted reproduction programs e.g. IVF
  A starting dose of 150-225 I.U. is recommended for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their 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.
  When a sufficient number of follicles of adequate size are present, the final phase of maturation of the follicles is induced by administration of hCG. Oocyte (egg) retrieval is performed 34-35 hours later.

METHOD AND ROUTE OF ADMINISTRATION - how injections are given
Puregon® only works if it is injected in a muscle or under the skin.
The very first injection of Puregon® should only be given under medical supervision.
The dry powder should be dissolved with the solvent contained in the ampoule with fluid and this solution should be administered immediately.

To avoid injection of large volumes 3 to 4 lyospheres of Puregon® may be dissolved in 1 ml of solvent. When only 1 or 2 lyospheres are required the volume may be reduced to 0.5 ml.

The injections are given slowly into a muscle (for instance in the buttock, upper leg or upper arm) or just under the skin (in the abdominal wall, for example). Injections into a muscle should only be given by a doctor or a nurse. Subcutaneous injections may, in some cases, be given by you or your partner. Your doctor will tell you when and how to do this.

If you administer Puregon® to yourself, follow the instructions below carefully and Puregon® will be administered properly and with minimal discomfort.

**Step 1 - Preparing Puregon®**

Puregon® comes in two glass ampoules whose contents must be mixed together. First, break the top off the ampoule with the sodium chloride solution (a, b). Draw up the liquid through the needle into the syringe (c). Break open the second ampoule containing the freeze-dried sphere (with the black dot in the position as indicated in the figures a and b) and add the sodium chloride solution from the syringe (d). DO NOT SHAKE, but gently swirl until the solution is clear. Generally the Puregon® dissolves immediately. Should the solution contain particles or not become clear, do not use.

If you need to dissolve more than one freeze-dried sphere, then repeat the actions described under points c and d until the required number of freeze-dried spheres is dissolved. Please make sure that all handling is performed in such a way that sterile conditions are maintained during the dissolution procedure (e.g. do not put the syringe down without covering the needle with the protective cap).

Draw the Puregon® solution up into the empty syringe (e), and now replace the needle with a sterile injection needle (f). 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 (g).

**Step 2 - The injection site**

**Intramuscular injection**

The best site for intramuscular injection of Puregon® is the buttock muscle. The area indicated in the diagram (the upper, outer quadrant) contains a large volume of muscle with few blood vessels or major nerves. Stretching the skin helps the needle to go in more easily and pushes the tissue beneath the skin out of the way. This helps the solution to disperse correctly.

**Subcutaneous injection**

The best site for subcutaneous injection is in the abdomen around the navel where there is a lot of loose skin and layers of fatty tissue. Pinch up a large area of skin between the finger and thumb. 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**
**Intramuscular:** The needle should be inserted right up to the hilt at an angle of 90° to the skin surface. Pushing in with a quick thrust causes least discomfort.

**Subcutaneous:** The needle should be inserted at the base of the pinched-up skin at an angle of 45° to the skin surface.

*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 new ampoules of Puregon® and sodium chloride solution.

*Step 6 - Injecting the solution*

Depress the plunger slowly and steadily, so the solution is correctly injected and the muscle or 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.

Any remaining solution should be discarded.

Do not mix Puregon® solution with any other medicines.

**OVERDOSE**

Too high a dose may cause overstimulation of the ovaries. See Section on Undesirable Effects below.

**UNDESIRABLE EFFECTS - unwanted effects**

A serious complication with FSH is unwanted overstimulation of the ovaries. This condition is rare, and the risk can be reduced by careful monitoring of follicle development during treatment. The first symptoms of ovarian overstimulation may be noticed as pain in the abdomen, feeling sick or diarrhoea. In more severe cases symptoms may include enlargement of the ovaries, accumulation of fluid in the abdomen and/or chest, weight gain and the occurrence of blood clots in the circulation. Contact your doctor without delay if you are experiencing any of these symptoms, also if they develop some days after the last injection has been given.

Minor side effects include bruising, pain, redness, swelling and itching at the site of the injection.

**SHELF LIFE AND STORAGE PRECAUTIONS - looking after your medicine**

Keep Puregon® in the original box in a safe place out of the reach of children.

Puregon should be stored below 30°C and protected from light. Do not freeze.

The expiry date is printed on the box after 'Use by:' and on the label after 'Exp.'. Do not use Puregon® after this date.

Any unused solution should be discarded.

This information was last updated in

**GENERAL THINGS TO REMEMBER ABOUT MEDICINES**

1. This medicine has been prescribed only for your current medical problem. It should not be used for other medical conditions.
2. Never give your medicine to anyone else and do not use medicines meant for other people.
3. Tell your doctor treating you which medicines you are currently taking. Always carry a medical information card stating which medicines you are using. This can be very important in case you are involved in an accident.
4. Return unused medicines to the pharmacy for disposal.
5. Make sure that the people you live with or who look after you read this information.
WHAT YOU SHOULD KNOW ABOUT PUREGON®

Please read the following information carefully before using this medicine. The leaflet contains details about Puregon®, as well as some general advice on using medicines. If you have any questions or other concerns, please ask your doctor or pharmacist.

NAME OF YOUR MEDICINE
The medicine prescribed for you is called Puregon®.

COMPOSITION AND STRENGTH - what your medicine contains
Puregon® 150 I.U. contains a hormone known as follicle-stimulating hormone (or FSH) in a strength of 150 I.U. per ampoule. Besides FSH, the powder contains sucrose, sodium citrate, and polysorbate 20; the solvent contains sodium chloride (4.5mg) and water for injections (1.0ml).

PHARMACEUTICAL FORM - what your medicine consists of
Puregon® 150 I.U. is supplied in a glass ampoule as a dry powder, which should be dissolved with the solvent contained in a second glass ampoule. It is available in packs of 1, 3, 5 and 10 ampoules.

THERAPEUTIC GROUP - how your medicine works
Gonadotropins (including FSH) play an important role in human fertility and reproduction. FSH is needed in women for the growth and development of follicles in the ovaries. Follicles are small round sacs that contain the egg cells.

MARKETING AUTHORISATION HOLDER
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands

MANUFACTURERS
Organon (Ireland) Ltd, P.O. Box 2857, Swords, Co. Dublin, Ireland
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands
Organon Laboratories Ltd, Newhouse, Lanarkshire, ML1 5SH, Scotland

INDICATIONS - when your medicine is used
Puregon® is used to treat infertility in either of the following situations:
• In women who are not ovulating, Puregon® can be used to cause ovulation in women who have not responded to treatment with clomiphene citrate.
• In women undergoing assisted reproduction techniques (ART), including in-vitro fertilisation (IVF) and other methods, Puregon® can be used to bring about the development of multiple follicles.

CONTRAINDICATIONS - when you should not use this medicine
There are certain medical conditions in which Puregon® should not be used. Do not use Puregon® if you:
• have a tumour of the ovary, breast, uterus, pituitary gland or hypothalamus.
• are pregnant or breast-feeding.
• are allergic to any of the substances of Puregon®.
• have heavy or irregular vaginal bleeding where the cause is not known.
• have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD).

This medicine should not be used when a condition exists which makes a normal pregnancy impossible. This may occur with primary ovarian failure, when there are fibroids in the uterus or when certain malformations of the sexual organs are present.
SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Caution
Close supervision of patients by a doctor is very important. Usually ultrasound scans of the ovaries are regularly made, and blood or urine samples are regularly taken. The results of these tests allow the doctor to choose the correct dose of Puregon® from day to day. This is very important since too high a dose of FSH may lead to rare but serious complications in which the ovaries become overstimulated. This may be noticed as pain in the abdomen. Regular monitoring of the response to FSH-treatment helps the doctor to prevent ovarian overstimulation. So contact your doctor without delay if you are experiencing significant abdominal pain, also if this occurs some days after the last injection has been given.

INTERACTIONS - when you are taking other medicines
If Puregon® is used in combination with clomiphene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Puregon® may be needed to achieve a response.

PREGNANCY AND LACTATION - When you are pregnant or breast-feeding
You should not be given Puregon® if you are already pregnant, or suspect that you might be pregnant, or if you are breast-feeding.
In pregnancies occurring after treatment with gonadotropic preparations, there is an increased risk of having twins or multiplets. There is a slightly increased risk of ectopic pregnancy in women with damaged fallopian tubes.
In women undergoing fertility treatment, there is a slightly higher risk of miscarriage.

ABILITY TO DRIVE OR OPERATE MACHINERY
As far as is known, Puregon® has no effect on alertness and concentration.

DOSAGE - the amount of medicine given
Your doctor will decide on the dose of Puregon® to be given. Usually treatment starts with 75 to 225 I.U. FSH each day. This dose may be increased as your treatment progresses. Further details of 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, follicle growth is checked by means of ultrasound scanning and measurement of the amount of estradiol (female sex hormone) in blood or urine. The dosage recommendations given below are in line with those usually applied for urinary FSH.
• Women who are not ovulating
  Treatment usually starts with the administration of 75 I.U. FSH per day. The starting 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 estradiol levels indicate an adequate response. The daily dose is then maintained until a follicle of adequate size is present. Usually 7 to 14 days of treatment are sufficient. The administration of Puregon® is then stopped and ovulation can be induced by administering human chorionic gonadotropin (hCG).
• Medically assisted reproduction programs e.g. IVF
  A starting dose of 150-225 I.U. is recommended for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their 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.
  When a sufficient number of follicles of adequate size are present, the final phase of maturation of the follicles is induced by administration of hCG. Oocyte (egg) retrieval is performed 34-35 hours later.

METHOD AND ROUTE OF ADMINISTRATION - how injections are given
Puregon® only works if it is injected in a muscle or under the skin.
The very first injection of Puregon® should only be given under medical supervision.
The dry powder should be dissolved with the solvent contained in the ampoule with fluid and this solution should be administered immediately.

To avoid injection of large volumes 3 to 4 lyospheres of Puregon® may be dissolved in 1 ml of solvent. When only 1 or 2 lyospheres are required the volume may be reduced to 0.5 ml.

The injections are given slowly into a muscle (for instance in the buttock, upper leg or upper arm) or just under the skin (in the abdominal wall, for example). Injections into a muscle should only be given by a doctor or a nurse. Subcutaneous injections may, in some cases, be given by you or your partner. Your doctor will tell you when and how to do this.

If you administer Puregon® to yourself, follow the instructions below carefully and Puregon® will be administered properly and with minimal discomfort.

**Step1 - Preparing Puregon®**

Puregon® comes in two glass ampoules whose contents must be mixed together. First, break the top off the ampoule with the sodium chloride solution (a, b). Draw up the liquid through the needle into the syringe (c). Break open the second ampoule containing the freeze-dried sphere (with the black dot in the position as indicated in the figures a and b) and add the sodium chloride solution from the syringe (d). DO NOT SHAKE, but gently swirl until the solution is clear. Generally the Puregon® dissolves immediately. Should the solution contain particles or not become clear, do not use.

If you need to dissolve more than one freeze-dried sphere, then repeat the actions described under points c and d until the required number of freeze-dried spheres is dissolved. Please make sure that all handling is performed in such a way that sterile conditions are maintained during the dissolution procedure (e.g. do not put the syringe down without covering the needle with the protective cap).

Draw the Puregon® solution up into the empty syringe (e), and now replace the needle with a sterile injection needle (f). 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 (g).

**Step2 - The injection site**

**Intramuscular injection**

The best site for intramuscular injection of Puregon® is the buttock muscle. The area indicated in the diagram (the upper, outer quadrant) contains a large volume of muscle with few blood vessels or major nerves. Stretching the skin helps the needle to go in more easily and pushes the tissue beneath the skin out of the way. This helps the solution to disperse correctly.

**Subcutaneous injection**

The best site for subcutaneous injection is in the abdomen around the navel where there is a lot of loose skin and layers of fatty tissue. Pinch up a large area of skin between the finger and thumb. 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.

**Step3 - 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.

**Step4 - Inserting the needle**
**Intramuscular:** The needle should be inserted right up to the hilt at an angle of 90° to the skin surface. Pushing in with a quick thrust causes least discomfort.

**Subcutaneous:** The needle should be inserted at the base of the pinched-up skin at an angle of 45° to the skin surface.

*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 new ampoules of Puregon® and sodium chloride solution.

*Step 6 - Injecting the solution*

Depress the plunger slowly and steadily, so the solution is correctly injected and the muscle or 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.

Any remaining solution should be discarded.

Do not mix Puregon® solution with any other medicines.

**OVERDOSE**

Too high a dose may cause overstimulation of the ovaries. See Section on Undesirable Effects below.

**UNDESIRABLE EFFECTS - unwanted effects**

A serious complication with FSH is unwanted overstimulation of the ovaries. This condition is rare, and the risk can be reduced by careful monitoring of follicle development during treatment. The first symptoms of ovarian overstimulation may be noticed as pain in the abdomen, feeling sick or diarrhoea. In more severe cases symptoms may include enlargement of the ovaries, accumulation of fluid in the abdomen and/or chest, weight gain and the occurrence of blood clots in the circulation. Contact your doctor without delay if you are experiencing any of these symptoms, also if they develop some days after the last injection has been given.

Minor side effects include bruising, pain, redness, swelling and itching at the site of the injection.

**SHELF LIFE AND STORAGE PRECAUTIONS - looking after your medicine**

Keep Puregon® in the original box in a safe place out of the reach of children.

Puregon should be stored below 30°C and protected from light. Do not freeze.

The expiry date is printed on the box after ‘Use by: ’ and on the label after ‘Exp.’. Do not use Puregon® after this date.

Any unused solution should be discarded.

This information was last updated in

**GENERAL THINGS TO REMEMBER ABOUT MEDICINES**

1. This medicine has been prescribed only for your current medical problem. It should not be used for other medical conditions.
2. Never give your medicine to anyone else and do not use medicines meant for other people.
3. Tell your doctor treating you which medicines you are currently taking. Always carry a medical information card stating which medicines you are using. This can be very important in case you are involved in an accident.
4. Return unused medicines to the pharmacy for disposal.
5. Make sure that the people you live with or who look after you read this information.