ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
Fertavid 50 IU/0.5 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains 50 IU recombinant follicle-stimulating hormone (FSH) in 0.5 ml aqueous solution. This corresponds to a strength of 100 IU/ml. One vial contains 5 microgram of protein (specific in vivo bioactivity equal to approximately 10 000 IU FSH / mg protein). The solution for injection contains the active substance follitropin beta, produced by genetic engineering of a Chinese hamster ovary (CHO) cell line.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

*In the female:*  
Fertavid 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 clomifene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs [e.g. *in vitro* fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)].

*In the male:*
- Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

4.2 Posology and method of administration

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

*Posology*

*Dosage in the female*  
There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasonography and monitoring of oestradiol levels.

Based on the results of comparative clinical studies, it is considered appropriate to give a lower dosage of Fertavid than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation.

Clinical experience with Fertavid is based on up to three treatment cycles in both indications. Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.
• **Anovulation**
A sequential treatment scheme is recommended starting with daily administration of 50 IU Fertavid. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol levels of 40-100% is considered to be optimal. The daily dose is then maintained until pre-ovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/ml (1000-3000 pmol/l) are attained. Usually, 7 to 14 days of treatment is sufficient to reach this state. The administration of Fertavid is then discontinued and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased.

Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided in order to prevent multiple gestations.

• **Controlled ovarian hyperstimulation in medically assisted reproduction programs**
Various stimulation protocols are applied. A starting dose of 100-225 IU is recommended for at least the first four days. Thereafter, the dose may be adjusted individually, based upon ovarian response. In clinical studies it was shown that maintenance dosages ranging from 75-375 IU for six to twelve days are sufficient, although longer treatment may be necessary. Fertavid can be given either alone, or, to prevent premature luteinisation, in combination with a GnRH agonist or antagonist. When using a GnRH agonist, a higher total treatment dose of Fertavid may be required to achieve an adequate follicular response.

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

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

There is no relevant indication for use of Fertavid in children.

**Method of administration**
To prevent painful injections and minimise leakage from the injection site Fertavid 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 Fertavid may be carried out by patient or partner, provided that proper instructions are given by the physician. Self administration of Fertavid should only be performed by patients who are well-motivated, adequately trained and with access to expert advice.

### 4.3 Contraindications

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

4.4 Special warnings and 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. Appropriate FSH dose adjustment(s) should prevent multiple follicle development. Multiple gestation, especially high order, carries an increased risk of adverse maternal and perinatal outcomes. The patients should be advised of the potential risks of multiple births before starting treatment.
• The first injection of Fertavid should be performed under direct medical supervision.
• Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
• Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.
• The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g., maternal age, sperm characteristics) and multiple gestations.
• 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 Fertavid should be discontinued. In that case pregnancy should be avoided and hCG must be withheld, because it may induce, in addition to multiple ovulation, the ovarian hyperstimulation syndrome (OHSS). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with ovarian hyperstimulation syndrome. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.
• There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.
• Women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m2) or thrombophilia, may have an increased risk of venous or arterial thrombo-embolic events, during or following treatment with gonadotrophins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
• Fertavid may contain traces of streptomycin and/or neomycin. These antibiotics may cause hypersensitivity reactions in susceptible persons.
• Elevated endogeneous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to Fertavid/hCG therapy.
• In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.
4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

There is no indication for use of Fertavid during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotropins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Fertavid should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical use of Fertavid by the intramuscular or subcutaneous routes may lead to local reactions at the site of injection: bruising, pain, redness, swelling and itching are commonly reported (3% of all patients treated). The majority of these local reactions are mild and transient in nature. Generalised hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.1% of all patients treated with Fertavid).

Treatment of women:

In approximately 4% of the women treated with Fertavid in clinical trials, signs and symptoms related to ovarian hyperstimulation syndrome (OHSS) have been reported (see section 4.4). Other undesirable effects related to this syndrome were observed in clinical studies. These include pelvic pain and/or congestion, abdominal pain and/or distension, breast complaints (breast tenderness, pain and/or engorgement), ovarian enlargement, and spontaneous abortion. They were all reported at an incidence of approximately 1% (pelvic pain and abdominal distension) or less.

A slightly increased risk of ectopic pregnancy and multiple gestations has been seen. Other more general symptoms that have been reported include headache and nausea (in up to 1% of the women treated with Fertavid).

In rare instances, thromboembolism has been associated with Fertavid/hCG therapy as with other gonadotrophins.

Treatment of men:

Gynaecomastia and acne may occur occasionally during Fertavid/hCG therapy. These are known effects of hCG treatment. In one subject an epididymal cyst was observed.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: gonadotrophins; ATC code: G03G A06.

Fertavid 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. Fertavid can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore Fertavid 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 Fertavid is generally followed by administration of hCG to induce the final phase of follicle maturation, resumption of meiosis and rupture of the follicle.

In men deficient in FSH, Fertavid should be used concomitantly with hCG for at least four months to promote spermatogenesis.

5.2 Pharmacokinetic properties

After intramuscular or subcutaneous administration of Fertavid, maximum concentrations of FSH are reached within about 12 hours. After intramuscular administration of Fertavid, the maximum FSH concentrations are higher and reached earlier in men as compared to women. 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 Fertavid. Both have an absolute bioavailability of approximately 77%. 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 Fertavid 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, Fertavid induced no toxicologically significant effects. Fertavid showed no mutagenic potential in the Ames test and in the in vitro chromosome aberration test with human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fertavid solution for injection contains:
sucrose
sodium citrate
L-methionine
polysorbate 20
water for injections.
The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

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

6.3 Shelf-life

3 years.

The contents of a vial should be used immediately after piercing of the rubber stopper.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial(s) in the outer carton.
For patient convenience, Fertavid may be stored at or below 25 ºC by the patient for a single period of not more than 3 months.

6.5 Nature and contents of container

0.5 ml of solution in 3 ml vial (type I glass) with stopper (chlorobutyl rubber).
Pack of 1, 5 or 10.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not use if the solution contains particles or if the solution is not clear.
The contents of a vial should be used immediately after piercing of the rubber stopper.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/09/510/001
EU/1/09/510/002
EU/1/09/510/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 19 March 2009
Date of last renewal:

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

Fertavid 75 IU/0.5 ml solution for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

One vial contains 75 IU recombinant follicle-stimulating hormone (FSH) in 0.5 ml aqueous solution. This corresponds to a strength of 150 IU/ml. One vial contains 7.5 microgram of protein (specific *in vivo* bioactivity equal to approximately 10 000 IU FSH / mg protein). The solution for injection contains the active substance follitropin beta, produced by genetic engineering of a Chinese hamster ovary (CHO) cell line.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection.
Clear and colourless solution.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

*In the female:*

Fertavid 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 clomifene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs [e.g. *in vitro* fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)].

*In the male:*

- Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

4.2 **Posology and method of administration**

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

**Posology**

*Dosage in the female*

There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasonography and monitoring of oestradiol levels.

Based on the results of comparative clinical studies, it is considered appropriate to give a lower dosage of Fertavid than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation.

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

A sequential treatment scheme is recommended starting with daily administration of 50 IU Fertavid. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol levels of 40-100% is considered to be optimal. The daily dose is then maintained until pre-ovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/ml (1000-3000 pmol/l) are attained. Usually, 7 to 14 days of treatment is sufficient to reach this state. The administration of Fertavid is then discontinued and ovulation can be induced by administering human chorionic gonadotrophin (hCG). If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased. Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided in order to prevent multiple gestations.

• **Controlled ovarian hyperstimulation in medically assisted reproduction programs**

Various stimulation protocols are applied. A starting dose of 100-225 IU is recommended for at least the first four days. Thereafter, the dose may be adjusted individually, based upon ovarian response. In clinical studies it was shown that maintenance dosages ranging from 75-375 IU for six to twelve days are sufficient, although longer treatment may be necessary. Fertavid can be given either alone, or, to prevent premature luteinisation, in combination with a GnRH agonist or antagonist. When using a GnRH agonist, a higher total treatment dose of Fertavid may be required to achieve an adequate follicular response. Ovarian response is monitored by ultrasonography and measurement of plasma oestradiol levels. When ultrasonographic evaluation indicates the presence of at least three follicles of 16-20 mm, and there is evidence of a good oestradiol response (plasma levels of about 300-400 picograms/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.

**Dosage in the male**

Fertavid should be given at a dosage of 450 IU/week, preferably divided in 3 dosages of 150 IU, concomitantly with hCG. The treatment should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. If a patient has not responded after this period, the combination therapy may be continued; current clinical experience indicates that treatment for up to 18 months or longer may be necessary to achieve spermatogenesis.

There is no relevant indication for use of Fertavid in children.

**Method of administration**

To prevent painful injections and minimise leakage from the injection site Fertavid 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 Fertavid may be carried out by patient or partner, provided that proper instructions are given by the physician. Self-administration of Fertavid should only be performed by patients who are well-motivated, adequately trained and with access to expert advice.

### 4.3 Contraindications

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

4.4 **Special warnings and 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. Appropriate FSH dose adjustment(s) should prevent multiple follicle development. Multiple gestation, especially high order, carries an increased risk of adverse maternal and perinatal outcomes. The patients should be advised of the potential risks of multiple births before starting treatment.
- The first injection of Fertavid should be performed under direct medical supervision.
- Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
- Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.
- The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g., maternal age, sperm characteristics) and multiple gestations.
- 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 Fertavid should be discontinued. In that case pregnancy should be avoided and hCG must be withheld, because it may induce, in addition to multiple ovulation, the ovarian hyperstimulation syndrome (OHSS). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with ovarian hyperstimulation syndrome. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.
- There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.
- Women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m2) or thrombophilia, may have an increased risk of venous or arterial thrombo-embolic events, during or following treatment with gonadotrophins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
- Fertavid may contain traces of streptomycin and/or neomycin. These antibiotics may cause hypersensitivity reactions in susceptible persons.
- Elevated endogeneous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to Fertavid/hCG therapy.
- In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.
4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

There is no indication for use of Fertavid during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotropins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Fertavid should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical use of Fertavid by the intramuscular or subcutaneous routes may lead to local reactions at the site of injection: bruising, pain, redness, swelling and itching are commonly reported (3% of all patients treated). The majority of these local reactions are mild and transient in nature. Generalised hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.1% of all patients treated with Fertavid).

Treatment of women:
In approximately 4% of the women treated with Fertavid in clinical trials, signs and symptoms related to ovarian hyperstimulation syndrome (OHSS) have been reported (see section 4.4). Other undesirable effects related to this syndrome were observed in clinical studies. These include pelvic pain and/or congestion, abdominal pain and/or distension, breast complaints (breast tenderness, pain and/or engorgement), ovarian enlargement, and spontaneous abortion. They were all reported at an incidence of approximately 1% (pelvic pain and abdominal distension) or less.
A slightly increased risk of ectopic pregnancy and multiple gestations has been seen.
Other more general symptoms that have been reported include headache and nausea (in up to 1% of the women treated with Fertavid).
In rare instances, thromboembolism has been associated with Fertavid/hCG therapy as with other gonadotrophins.

Treatment of men:
Gynaecomastia and acne may occur occasionally during Fertavid/hCG therapy. These are known effects of hCG treatment. In one subject an epididymal cyst was observed.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: gonadotrophins; ATC code: G03G A06.

Fertavid 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. Fertavid can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore Fertavid 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 Fertavid is generally followed by administration of hCG to induce the final phase of follicle maturation, resumption of meiosis and rupture of the follicle.

In men deficient in FSH, Fertavid should be used concomitantly with hCG for at least four months to promote spermatogenesis.

5.2 Pharmacokinetic properties

After intramuscular or subcutaneous administration of Fertavid, maximum concentrations of FSH are reached within about 12 hours. After intramuscular administration of Fertavid, the maximum FSH concentrations are higher and reached earlier in men as compared to women. 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 Fertavid. Both have an absolute bioavailability of approximately 77%. 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 Fertavid 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, Fertavid induced no toxicologically significant effects. Fertavid showed no mutagenic potential in the Ames test and in the in vitro chromosome aberration test with human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fertavid solution for injection contains:
- sucrose
- sodium citrate
- L-methionine
- polysorbate 20
- water for injections.

The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

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

6.3 Shelf-life

3 years.

The contents of a vial should be used immediately after piercing of the rubber stopper.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial(s) in the outer carton.
For patient convenience, Fertavid may be stored at or below 25 ºC by the patient for a single period of not more than 3 months.

6.5 Nature and contents of container

0.5 ml of solution in 3 ml vial (type I glass) with stopper (chlorobutyl rubber).
Pack of 1, 5 or 10.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not use if the solution contains particles or if the solution is not clear.
The contents of a vial should be used immediately after piercing of the rubber stopper.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/09/510/004
EU/1/09/510/005
EU/1/09/510/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 19 March 2009
Date of last renewal:

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

Fertavid 100 IU/0.5 ml solution for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

One vial contains 100 IU recombinant follicle-stimulating hormone (FSH) in 0.5 ml aqueous solution. This corresponds to a strength of 200 IU/ml. One vial contains 10 microgram of protein (specific *in vivo* bioactivity equal to approximately 10 000 IU FSH / mg protein). The solution for injection contains the active substance follitropin beta, produced by genetic engineering of a Chinese hamster ovary (CHO) cell line.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection. Clear and colourless solution.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

*In the female:*

Fertavid 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 clomifene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs [e.g. *in vitro* fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)].

*In the male:*

- Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

4.2 **Posology and method of administration**

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

**Posology**

*Dosage in the female*

There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasonography and monitoring of oestriadiol levels.

Based on the results of comparative clinical studies, it is considered appropriate to give a lower dosage of Fertavid than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation.

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

A sequential treatment scheme is recommended starting with daily administration of 50 IU Fertavid. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol levels of 40-100% is considered to be optimal. The daily dose is then maintained until pre-ovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/ml (1000-3000 pmol/l) are attained. Usually, 7 to 14 days of treatment is sufficient to reach this state. The administration of Fertavid is then discontinued and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased.

Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided in order to prevent multiple gestations.

Controlled ovarian hyperstimulation in medically assisted reproduction programs

Various stimulation protocols are applied. A starting dose of 100-225 IU is recommended for at least the first four days. Thereafter, the dose may be adjusted individually, based upon ovarian response. In clinical studies it was shown that maintenance dosages ranging from 75-375 IU for six to twelve days are sufficient, although longer treatment may be necessary. Fertavid can be given either alone, or, to prevent premature luteinisation, in combination with a GnRH agonist or antagonist. When using a GnRH agonist, a higher total treatment dose of Fertavid may be required to achieve an adequate follicular response.

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

Dosage in the male

Fertavid should be given at a dosage of 450 IU/week, preferably divided in 3 dosages of 150 IU, concomitantly with hCG. The treatment should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. If a patient has not responded after this period, the combination therapy may be continued; current clinical experience indicates that treatment for up to 18 months or longer may be necessary to achieve spermatogenesis.

There is no relevant indication for use of Fertavid in children.

Method of administration

To prevent painful injections and minimise leakage from the injection site Fertavid 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 Fertavid may be carried out by patient or partner, provided that proper instructions are given by the physician. Self-administration of Fertavid should only be performed by patients who are well-motivated, adequately trained and with access to expert advice.

4.3 Contraindications

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

4.4 Special warnings and 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. Appropriate FSH dose adjustment(s) should prevent multiple follicle development. Multiple gestation, especially high order, carries an increased risk of adverse maternal and perinatal outcomes. The patients should be advised of the potential risks of multiple births before starting treatment.
• The first injection of Fertavid should be performed under direct medical supervision.
• Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
• Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.
• The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g., maternal age, sperm characteristics) and multiple gestations.
• 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 Fertavid should be discontinued. In that case pregnancy should be avoided and hCG must be withheld, because it may induce, in addition to multiple ovulation, the ovarian hyperstimulation syndrome (OHSS). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with ovarian hyperstimulation syndrome. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.
• There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.
• Women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m2) or thrombophilia, may have an increased risk of venous or arterial thrombo-embolic events, during or following treatment with gonadotrophins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
• Fertavid may contain traces of streptomycin and/or neomycin. These antibiotics may cause hypersensitivity reactions in susceptible persons.
• Elevated endogeneous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to Fertavid/hCG therapy.
• In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.
4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

There is no indication for use of Fertavid during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotropins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Fertavid should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical use of Fertavid by the intramuscular or subcutaneous routes may lead to local reactions at the site of injection: bruising, pain, redness, swelling and itching are commonly reported (3% of all patients treated). The majority of these local reactions are mild and transient in nature. Generalised hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.1% of all patients treated with Fertavid).

Treatment of women:
In approximately 4% of the women treated with Fertavid in clinical trials, signs and symptoms related to ovarian hyperstimulation syndrome (OHSS) have been reported (see section 4.4). Other undesirable effects related to this syndrome were observed in clinical studies. These include pelvic pain and/or congestion, abdominal pain and/or distension, breast complaints (breast tenderness, pain and/or engorgement), ovarian enlargement, and spontaneous abortion. They were all reported at an incidence of approximately 1% (pelvic pain and abdominal distension) or less.

A slightly increased risk of ectopic pregnancy and multiple gestations has been seen.

Other more general symptoms that have been reported include headache and nausea (in up to 1% of the women treated with Fertavid).

In rare instances, thromboembolism has been associated with Fertavid/hCG therapy as with other gonadotrophins.

Treatment of men:
Gynaecomastia and acne may occur occasionally during Fertavid/hCG therapy. These are known effects of hCG treatment. In one subject an epididymal cyst was observed.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: gonadotrophins; ATC code: G03G A06.

Fertavid 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. Fertavid can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore Fertavid 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 Fertavid is generally followed by administration of hCG to induce the final phase of follicle maturation, resumption of meiosis and rupture of the follicle.

In men deficient in FSH, Fertavid should be used concomitantly with hCG for at least four months to promote spermatogenesis.

5.2 Pharmacokinetic properties

After intramuscular or subcutaneous administration of Fertavid, maximum concentrations of FSH are reached within about 12 hours. After intramuscular administration of Fertavid, the maximum FSH concentrations are higher and reached earlier in men as compared to women. 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 Fertavid. Both have an absolute bioavailability of approximately 77%. 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 Fertavid 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, Fertavid induced no toxicologically significant effects. Fertavid showed no mutagenic potential in the Ames test and in the in vitro chromosome aberration test with human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fertavid solution for injection contains:
sucrose
sodium citrate
L-methionine
polysorbate 20
water for injections.
The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

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

6.3 Shelf-life

3 years.

The contents of a vial should be used immediately after piercing of the rubber stopper.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial(s) in the outer carton.
For patient convenience, Fertavid may be stored at or below 25 ºC by the patient for a single period of not more than 3 months.

6.5 Nature and contents of container

0.5 ml of solution in 3 ml vial (type I glass) with stopper (chlorobutyl rubber).
Pack of 1, 5 or 10.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not use if the solution contains particles or if the solution is not clear.
The contents of a vial should be used immediately after piercing of the rubber stopper.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/09/510/007
EU/1/09/510/008
EU/1/09/510/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 19 March 2009
Date of last renewal:

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

Fertavid 150 IU/0.5 ml solution for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

One vial contains 150 IU recombinant follicle-stimulating hormone (FSH) in 0.5 ml aqueous solution. This corresponds to a strength of 300 IU/ml. One vial contains 15 microgram of protein (specific in vivo bioactivity equal to approximately 10 000 IU FSH / mg protein). The solution for injection contains the active substance follitropin beta, produced by genetic engineering of a Chinese hamster ovary (CHO) cell line.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection. Clear and colourless solution.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

*In the female:*
Fertavid 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 clomifene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs [e.g. *in vitro* fertilisation/embryo transfer (IVF/ET), gamete intrafallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)].

*In the male:*
- Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

4.2 **Posology and method of administration**

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

*Posology*

*Dosage in the female*
There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasonography and monitoring of oestradiol levels. Based on the results of comparative clinical studies, it is considered appropriate to give a lower dosage of Fertavid than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation. Clinical experience with Fertavid is based on up to three treatment cycles in both indications. Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.
- **Anovulation**
  A sequential treatment scheme is recommended starting with daily administration of 50 IU Fertavid. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol levels of 40-100% is considered to be optimal. The daily dose is then maintained until pre-ovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/ml (1000-3000 pmol/l) are attained. Usually, 7 to 14 days of treatment is sufficient to reach this state. The administration of Fertavid is then discontinued and ovulation can be induced by administering human chorionic gonadotrophin (hCG). If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased. Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided in order to prevent multiple gestations.

- **Controlled ovarian hyperstimulation in medically assisted reproduction programs**
  Various stimulation protocols are applied. A starting dose of 100-225 IU is recommended for at least the first four days. Thereafter, the dose may be adjusted individually, based upon ovarian response. In clinical studies it was shown that maintenance dosages ranging from 75-375 IU for six to twelve days are sufficient, although longer treatment may be necessary. Fertavid can be given either alone, or, to prevent premature luteinisation, in combination with a GnRH agonist or antagonist. When using a GnRH agonist, a higher total treatment dose of Fertavid may be required to achieve an adequate follicular response. Ovarian response is monitored by ultrasonography and measurement of plasma oestradiol levels. When ultrasonographic evaluation indicates the presence of at least three follicles of 16-20 mm, and there is evidence of a good oestradiol response (plasma levels of about 300-400 picograms/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.

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

There is no relevant indication for use of Fertavid in children.

**Method of administration**
To prevent painful injections and minimise leakage from the injection site Fertavid 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 Fertavid may be carried out by patient or partner, provided that proper instructions are given by the physician. Self-administration of Fertavid should only be performed by patients who are well-motivated, adequately trained and with access to expert advice.

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

4.4 Special warnings and 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. Appropriate FSH dose adjustment(s) should prevent multiple follicle development. Multiple gestation, especially high order, carries an increased risk of adverse maternal and perinatal outcomes. The patients should be advised of the potential risks of multiple births before starting treatment.
• The first injection of Fertavid should be performed under direct medical supervision.
• Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
• Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.
• The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g., maternal age, sperm characteristics) and multiple gestations.
• 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 Fertavid should be discontinued. In that case pregnancy should be avoided and hCG must be withheld, because it may induce, in addition to multiple ovulation, the ovarian hyperstimulation syndrome (OHSS). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with ovarian hyperstimulation syndrome. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.
• There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.
• Women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m2) or thrombophilia, may have an increased risk of venous or arterial thrombo-embolic events, during or following treatment with gonadotrophins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
• Fertavid may contain traces of streptomycin and/or neomycin. These antibiotics may cause hypersensitivity reactions in susceptible persons.
• Elevated endogeneous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to Fertavid/hCG therapy.
• In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.
4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

There is no indication for use of Fertavid during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotropins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Fertavid should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical use of Fertavid by the intramuscular or subcutaneous routes may lead to local reactions at the site of injection: bruising, pain, redness, swelling and itching are commonly reported (3% of all patients treated). The majority of these local reactions are mild and transient in nature. Generalised hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.1% of all patients treated with Fertavid).

Treatment of women:
In approximately 4% of the women treated with Fertavid in clinical trials, signs and symptoms related to ovarian hyperstimulation syndrome (OHSS) have been reported (see section 4.4). Other undesirable effects related to this syndrome were observed in clinical studies. These include pelvic pain and/or congestion, abdominal pain and/or distension, breast complaints (breast tenderness, pain and/or engorgement), ovarian enlargement, and spontaneous abortion. They were all reported at an incidence of approximately 1% (pelvic pain and abdominal distension) or less.
A slightly increased risk of ectopic pregnancy and multiple gestations has been seen.
Other more general symptoms that have been reported include headache and nausea (in up to 1% of the women treated with Fertavid).
In rare instances, thromboembolism has been associated with Fertavid/hCG therapy as with other gonadotrophins.

Treatment of men:
Gynaecomastia and acne may occur occasionally during Fertavid/hCG therapy. These are known effects of hCG treatment. In one subject an epididymal cyst was observed.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Fertavid 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. Fertavid can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore Fertavid 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 Fertavid is generally followed by administration of hCG to induce the final phase of follicle maturation, resumption of meiosis and rupture of the follicle.

In men deficient in FSH, Fertavid should be used concomitantly with hCG for at least four months to promote spermatogenesis.

### 5.2 Pharmacokinetic properties

After intramuscular or subcutaneous administration of Fertavid, maximum concentrations of FSH are reached within about 12 hours. After intramuscular administration of Fertavid, the maximum FSH concentrations are higher and reached earlier in men as compared to women. 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 Fertavid. Both have an absolute bioavailability of approximately 77%. 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 Fertavid 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, Fertavid induced no toxicologically significant effects. Fertavid showed no mutagenic potential in the Ames test and in the *in vitro* chromosome aberration test with human lymphocytes.

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

Fertavid solution for injection contains:
- sucrose
- sodium citrate
- L-methionine
- polysorbate 20
- water for injections.

The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

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

6.3 Shelf-life

3 years.

The contents of a vial should be used immediately after piercing of the rubber stopper.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial(s) in the outer carton.
For patient convenience, Fertavid may be stored at or below 25 ºC by the patient for a single period of not more than 3 months.

6.5 Nature and contents of container

0.5 ml of solution in 3 ml vial (type I glass) with stopper (chlorobutyl rubber).
Pack of 1, 5 or 10.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not use if the solution contains particles or if the solution is not clear.
The contents of a vial should be used immediately after piercing of the rubber stopper.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/09/510/010
EU/1/09/510/011
EU/1/09/510/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 19 March 2009
Date of last renewal:

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

Fertavid 200 IU/0.5 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 200 IU recombinant follicle-stimulating hormone (FSH) in 0.5 ml aqueous solution. This corresponds to a strength of 400 IU/ml. One vial contains 20 microgram of protein (specific in vivo bioactivity equal to approximately 10 000 IU FSH / mg protein). The solution for injection contains the active substance follitropin beta, produced by genetic engineering of a Chinese hamster ovary (CHO) cell line.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In the female:
Fertavid 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 clomifene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs [e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intracellular transfer (GIFT) and intracytoplasmic sperm injection (ICSI)].

In the male:
- Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

4.2 Posology and method of administration

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

Posology

Dosage in the female
There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasonography and monitoring of oestradiol levels.

Based on the results of comparative clinical studies, it is considered appropriate to give a lower dosage of Fertavid than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation.

Clinical experience with Fertavid is based on up to three treatment cycles in both indications. Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.
• **Anovulation**
A sequential treatment scheme is recommended starting with daily administration of 50 IU Fertavid. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol levels of 40-100% is considered to be optimal. The daily dose is then maintained until pre-ovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/ml (1000-3000 pmol/l) are attained. Usually, 7 to 14 days of treatment is sufficient to reach this state. The administration of Fertavid is then discontinued and ovulation can be induced by administering human chorionic gonadotrophin (hCG). If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased. Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided in order to prevent multiple gestations.

• **Controlled ovarian hyperstimulation in medically assisted reproduction programs**
Various stimulation protocols are applied. A starting dose of 100-225 IU is recommended for at least the first four days. Thereafter, the dose may be adjusted individually, based upon ovarian response. In clinical studies it was shown that maintenance dosages ranging from 75-375 IU for six to twelve days are sufficient, although longer treatment may be necessary. Fertavid can be given either alone, or, to prevent premature luteinisation, in combination with a GnRH agonist or antagonist. When using a GnRH agonist, a higher total treatment dose of Fertavid may be required to achieve an adequate follicular response. Ovarian response is monitored by ultrasonography and measurement of plasma oestradiol levels. When ultrasonographic evaluation indicates the presence of at least three follicles of 16-20 mm, and there is evidence of a good oestradiol response (plasma levels of about 300-400 picograms/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.

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

There is no relevant indication for use of Fertavid in children.

**Method of administration**
To prevent painful injections and minimise leakage from the injection site Fertavid 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 Fertavid may be carried out by patient or partner, provided that proper instructions are given by the physician. Self administration of Fertavid should only be performed by patients who are well-motivated, adequately trained and with access to expert advice.

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

4.4 Special warnings and 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. Appropriate FSH dose adjustment(s) should prevent multiple follicle development. Multiple gestation, especially high order, carries an increased risk of adverse maternal and perinatal outcomes. The patients should be advised of the potential risks of multiple births before starting treatment.
• The first injection of Fertavid should be performed under direct medical supervision.
• Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
• Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.
• The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g., maternal age, sperm characteristics) and multiple gestations.
• 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 Fertavid should be discontinued. In that case pregnancy should be avoided and hCG must be withheld, because it may induce, in addition to multiple ovulation, the ovarian hyperstimulation syndrome (OHSS). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with ovarian hyperstimulation syndrome. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.
• There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.
• Women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m2) or thrombophilia, may have an increased risk of venous or arterial thrombo-embolic events, during or following treatment with gonadotrophins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
• Fertavid may contain traces of streptomycin and/or neomycin. These antibiotics may cause hypersensitivity reactions in susceptible persons.
• Elevated endogeneous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to Fertavid/hCG therapy.
• In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.
4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

There is no indication for use of Fertavid during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotropins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Fertavid should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical use of Fertavid by the intramuscular or subcutaneous routes may lead to local reactions at the site of injection: bruising, pain, redness, swelling and itching are commonly reported (3% of all patients treated). The majority of these local reactions are mild and transient in nature. Generalised hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.1% of all patients treated with Fertavid).

Treatment of women:
In approximately 4% of the women treated with Fertavid in clinical trials, signs and symptoms related to ovarian hyperstimulation syndrome (OHSS) have been reported (see section 4.4). Other undesirable effects related to this syndrome were observed in clinical studies. These include pelvic pain and/or congestion, abdominal pain and/or distension, breast complaints (breast tenderness, pain and/or engorgement), ovarian enlargement, and spontaneous abortion. They were all reported at an incidence of approximately 1% (pelvic pain and abdominal distension) or less. A slightly increased risk of ectopic pregnancy and multiple gestations has been seen. Other more general symptoms that have been reported include headache and nausea (in up to 1% of the women treated with Fertavid).
In rare instances, thromboembolism has been associated with Fertavid/hCG therapy as with other gonadotrophins.

Treatment of men:
Gynaecomastia and acne may occur occasionally during Fertavid/hCG therapy. These are known effects of hCG treatment. In one subject an epididymal cyst was observed.

4.9 Overdose

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

5. PHARMAKOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: gonadotrophins; ATC code: G03G A06.

Fertavid 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. Fertavid can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore Fertavid 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 Fertavid is generally followed by administration of hCG to induce the final phase of follicle maturation, resumption of meiosis and rupture of the follicle.

In men deficient in FSH, Fertavid should be used concomitantly with hCG for at least four months to promote spermatogenesis.

5.2 Pharmacokinetic properties

After intramuscular or subcutaneous administration of Fertavid, maximum concentrations of FSH are reached within about 12 hours. After intramuscular administration of Fertavid, the maximum FSH concentrations are higher and reached earlier in men as compared to women. 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 Fertavid. Both have an absolute bioavailability of approximately 77%. 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 Fertavid 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, Fertavid induced no toxicologically significant effects. Fertavid showed no mutagenic potential in the Ames test and in the in vitro chromosome aberration test with human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fertavid solution for injection contains:
sucrose
sodium citrate
L-methionine
polysorbate 20
water for injections.
The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

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

6.3 Shelf-life

3 years.

The contents of a vial should be used immediately after piercing of the rubber stopper.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial(s) in the outer carton.
For patient convenience, Fertavid may be stored at or below 25 °C by the patient for a single period of not more than 3 months.

6.5 Nature and contents of container

0.5 ml of solution in 3 ml vial (type I glass) with stopper (chlorobutyl rubber).
Pack of 1, 5 or 10.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not use if the solution contains particles or if the solution is not clear.
The contents of a vial should be used immediately after piercing of the rubber stopper.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/09/510/013
EU/1/09/510/014
EU/1/09/510/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 19 March 2009
Date of last renewal:

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

Fertavid 150 IU/0.18 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear and colourless solution.
In cartridges, designed to be used in conjunction with a pen injector.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In the female:
Fertavid 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 clomifene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs [e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)].

In the male:
- Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

4.2 Posology and method of administration

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

Posology

Dosage in the female
There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasonography and monitoring of oestradiol levels.
When using the pen injector, it should be realised that the pen is a precision device which accurately delivers the dose to which it is set. It was shown that on average an 18% higher amount of FSH is given with the pen compared with a conventional syringe. This may be of particular relevance when switching between the pen injector and a conventional syringe within one treatment cycle. Especially when switching from a syringe to the pen, small dose adjustments may be needed to prevent too high a dose being given.
Based on the results of comparative clinical studies, it is considered appropriate to give a lower dosage of Fertavid than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation.

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

- **Anovulation**

  A sequential treatment scheme is recommended starting with daily administration of 50 IU Fertavid. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol levels of 40-100% is considered to be optimal. The daily dose is then maintained until pre-ovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/ml (1000-3000 pmol/l) are attained. Usually, 7 to 14 days of treatment is sufficient to reach this state. The administration of Fertavid is then discontinued and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

  If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased.

  Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided to prevent multiple gestations.

- **Controlled ovarian hyperstimulation in medically assisted reproduction programs**

  Various stimulation protocols are applied. A starting dose of 100-225 IU is recommended for at least the first four days. Thereafter, the dose may be adjusted individually, based upon ovarian response. In clinical studies it was shown that maintenance dosages ranging from 75-375 IU for six to twelve days are sufficient, although longer treatment may be necessary.

  Fertavid can be given either alone, or, to prevent premature luteinisation, in combination with a GnRH agonist or antagonist. When using a GnRH agonist, a higher total treatment dose of Fertavid may be required to achieve an adequate follicular response.

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

**Dosage in the male**

Fertavid should be given at a dosage of 450 IU/week, preferably divided in 3 dosages of 150 IU, concomitantly with hCG. The treatment should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. If a patient has not responded after this period, the combination therapy may be continued; current clinical experience indicates that treatment for up to 18 months or longer may be necessary to achieve spermatogenesis.

There is no relevant indication for use of Fertavid in children.

**Method of administration**

Fertavid solution for injection in cartridges has been developed for use in a pen injector called Puregon Pen and should be administered subcutaneously. The injection site should be alternated to prevent lipoatrophy.

Using the pen injector, injection of Fertavid can be carried out by the patient, provided that proper instructions are given by the physician.

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

4.4 Special warnings and 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. Appropriate FSH dose adjustment(s) should prevent multiple follicle development. Multiple gestation, especially high order, carries an increased risk of adverse maternal and perinatal outcomes. The patients should be advised of the potential risks of multiple births before starting treatment.
• The first injection of Fertavid should be performed under direct medical supervision.
• Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
• Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.
• The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g., maternal age, sperm characteristics) and multiple gestations.
• 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 Fertavid should be discontinued. In that case pregnancy should be avoided and hCG must be withheld, because it may induce, in addition to multiple ovulation, the ovarian hyperstimulation syndrome (OHSS). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with ovarian hyperstimulation syndrome. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.
• There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.
• Women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m²) or thrombophilia, may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotrophins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
• Fertavid may contain traces of streptomycin and/or neomycin. These antibiotics may cause hypersensitivity reactions in susceptible persons.
• Elevated endogenous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to Fertavid/hCG therapy.
• In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

There is no indication for use of Fertavid during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotropins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Fertavid should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical use of Fertavid by the intramuscular or subcutaneous routes may lead to local reactions at the site of injection: bruising, pain, redness, swelling and itching are commonly reported (3% of all patients treated). The majority of these local reactions are mild and transient in nature. Generalised hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.1% of all patients treated with Fertavid).

Treatment of women:
In approximately 4% of the women treated with Fertavid in clinical trials, signs and symptoms related to ovarian hyperstimulation syndrome (OHSS) have been reported (see section 4.4). Other undesirable effects related to this syndrome were observed in clinical studies. These include pelvic pain and/or congestion, abdominal pain and/or distension, breast complaints (breast tenderness, pain and/or engorgement), ovarian enlargement, and spontaneous abortion. They were all reported at an incidence of approximately 1% (pelvic pain and abdominal distension) or less. A slightly increased risk of ectopic pregnancy and multiple gestations has been seen. Other more general symptoms that have been reported include headache and nausea (in up to 1% of the women treated with Fertavid).
In rare instances, thromboembolism has been associated with Fertavid/hCG therapy as with other gonadotrophins.

Treatment of men:
Gynaecomastia and acne may occur occasionally during Fertavid/hCG therapy. These are known effects of hCG treatment. In one subject an epididymal cyst was observed.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: gonadotrophins; ATC code: G03G A06.

Fertavid 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. Fertavid can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore Fertavid 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 Fertavid is generally followed by administration of hCG to induce the final phase of follicle maturation, resumption of meiosis and rupture of the follicle.

In men deficient in FSH, Fertavid should be used concomitantly with hCG for at least four months to promote spermatogenesis.

5.2 Pharmacokinetic properties

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

The absolute bioavailability of subcutaneously administered Fertavid is approximately 77%. 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 Fertavid 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, Fertavid induced no toxicologically significant effects. Fertavid showed no mutagenic potential in the Ames test and in the in vitro chromosome aberration test with human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fertavid 150 IU/0.18 ml solution for injection contains:
sucrose
sodium citrate
L-methionine
polysorbate 20
benzyl alcohol
water for injections.
The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

6.2 Incompatibilities

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

6.3 Shelf-life

3 years.

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the cartridge in the outer carton.
For patient convenience, Fertavid may be stored at or below 25 ºC by the patient for a single period of not more than 3 months.

6.5 Nature and contents of container

0.18 ml of solution in 1.5 ml cartridge (type I glass) with a grey rubber piston and an aluminium crimp-cap with a rubber inlay.
Pack of 1 cartridge and 3 needles to be used with the Puregon Pen.
Cartridges contain a minimum of 225 IU FSH activity in 0.270 ml aqueous solution, which is sufficient for a net total dose of 150 IU.

6.6 Special precautions for disposal and other handling

Do not use if the solution contains particles or if the solution is not clear.
Fertavid 150 IU/0.18 ml solution for injection is designed for use in conjunction with a pen injector called Puregon Pen. The instructions for using the pen must be followed carefully.
Air bubbles must be removed from the cartridge before injection (see instructions for using the pen).
Empty cartridges must not be refilled.
Fertavid cartridges are not designed to allow any other drug to be mixed in the cartridges.
Discard used needles immediately after injection.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER

EU/1/09/510/016
9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 19 March 2009
Date of last renewal:

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

Fertavid 300 IU/0.36 ml solution for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection.
Clear and colourless solution.
In cartridges, designed to be used in conjunction with a pen injector.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

*In the female:*
Fertavid 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 clomifene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs [e.g. *in vitro* fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)].

*In the male:*
- Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

4.2 **Posology and method of administration**

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

**Posology**

*Dosage in the female*
There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasonography and monitoring of oestradiol levels.

When using the pen injector, it should be realised that the pen is a precision device which accurately delivers the dose to which it is set. It was shown that on average an 18% higher amount of FSH is given with the pen compared with a conventional syringe. This may be of particular relevance when switching between the pen injector and a conventional syringe within one treatment cycle. Especially when switching from a syringe to the pen, small dose adjustments may be needed to prevent too high a dose being given.
Based on the results of comparative clinical studies, it is considered appropriate to give a lower dosage of Fertavid than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation. Clinical experience with Fertavid is based on up to three treatment cycles in both indications. Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

- **Anovulation**
  A sequential treatment scheme is recommended starting with daily administration of 50 IU Fertavid. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol levels of 40-100% is considered to be optimal. The daily dose is then maintained until pre-ovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/ml (1000-3000 pmol/l) are attained. Usually, 7 to 14 days of treatment is sufficient to reach this state. The administration of Fertavid is then discontinued and ovulation can be induced by administering human chorionic gonadotrophin (hCG).
  If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased.
  Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided to prevent multiple gestations.

- **Controlled ovarian hyperstimulation in medically assisted reproduction programs**
  Various stimulation protocols are applied. A starting dose of 100-225 IU is recommended for at least the first four days. Thereafter, the dose may be adjusted individually, based upon ovarian response. In clinical studies it was shown that maintenance dosages ranging from 75-375 IU for six to twelve days are sufficient, although longer treatment may be necessary. Fertavid can be given either alone, or, to prevent premature luteinisation, in combination with a GnRH agonist or antagonist. When using a GnRH agonist, a higher total treatment dose of Fertavid may be required to achieve an adequate follicular response.
  Ovarian response is monitored by ultrasonography and measurement of plasma oestradiol levels. When ultrasonographic evaluation indicates the presence of at least three follicles of 16-20 mm, and there is evidence of a good oestradiol response (plasma levels of about 300-400 picograms/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.

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

There is no relevant indication for use of Fertavid in children.

*Method of administration*
Fertavid solution for injection in cartridges has been developed for use in a pen injector called Puregon Pen and should be administered subcutaneously. The injection site should be alternated to prevent lipoatrophy.
Using the pen injector, injection of Fertavid can be carried out by the patient, provided that proper instructions are given by the physician.

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

4.4 Special warnings and 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. Appropriate FSH dose adjustment(s) should prevent multiple follicle development. Multiple gestation, especially high order, carries an increased risk of adverse maternal and perinatal outcomes. The patients should be advised of the potential risks of multiple births before starting treatment.
• The first injection of Fertavid should be performed under direct medical supervision.
• Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
• Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.
• The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g., maternal age, sperm characteristics) and multiple gestations.
• 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 Fertavid should be discontinued. In that case pregnancy should be avoided and hCG must be withheld, because it may induce, in addition to multiple ovulation, the ovarian hyperstimulation syndrome (OHSS). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with ovarian hyperstimulation syndrome. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.
• There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.
• Women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m²) or thrombophilia, may have an increased risk of venous or arterial thrombo-embolic events, during or following treatment with gonadotrophins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
• Fertavid may contain traces of streptomycin and/or neomycin. These antibiotics may cause hypersensitivity reactions in susceptible persons.
• Elevated endogeneous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to Fertavid/hCG therapy.
• In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

There is no indication for use of Fertavid during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotropins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Fertavid should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical use of Fertavid by the intramuscular or subcutaneous routes may lead to local reactions at the site of injection: bruising, pain, redness, swelling and itching are commonly reported (3% of all patients treated). The majority of these local reactions are mild and transient in nature. Generalised hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.1% of all patients treated with Fertavid).

_Treatment of women:_
In approximately 4% of the women treated with Fertavid in clinical trials, signs and symptoms related to ovarian hyperstimulation syndrome (OHSS) have been reported (see section 4.4). Other undesirable effects related to this syndrome were observed in clinical studies. These include pelvic pain and/or congestion, abdominal pain and/or distension, breast complaints (breast tenderness, pain and/or engorgement), ovarian enlargement, and spontaneous abortion. They were all reported at an incidence of approximately 1% (pelvic pain and abdominal distension) or less.
A slightly increased risk of ectopic pregnancy and multiple gestations has been seen.
Other more general symptoms that have been reported include headache and nausea (in up to 1% of the women treated with Fertavid).
In rare instances, thromboembolism has been associated with Fertavid/hCG therapy as with other gonadotrophins.

_Treatment of men:_
Gynaecomastia and acne may occur occasionally during Fertavid/hCG therapy. These are known effects of hCG treatment. In one subject an epididymal cyst was observed.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: gonadotrophins; ATC code: G03G A06.

Fertavid 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. Fertavid can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore Fertavid 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 Fertavid is generally followed by administration of hCG to induce the final phase of follicle maturation, resumption of meiosis and rupture of the follicle.

In men deficient in FSH, Fertavid should be used concomitantly with hCG for at least four months to promote spermatogenesis.

5.2 Pharmacokinetic properties

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

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 Fertavid 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, Fertavid induced no toxicologically significant effects. Fertavid showed no mutagenic potential in the Ames test and in the in vitro chromosome aberration test with human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fertavid 300 IU/0.36 ml solution for injection contains:
sucrose
sodium citrate
L-methionine
polysorbate 20
benzyl alcohol
water for injections.
The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

6.2 Incompatibilities

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

6.3 Shelf-life

3 years.

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the cartridge in the outer carton.
For patient convenience, Fertavid may be stored at or below 25 °C by the patient for a single period of not more than 3 months.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Do not use if the solution contains particles or if the solution is not clear.
Fertavid 300 IU/0.36 ml solution for injection is designed for use in conjunction with a pen injector called Puregon Pen. The instructions for using the pen must be followed carefully.
Air bubbles must be removed from the cartridge before injection (see instructions for using the pen).
Empty cartridges must not be refilled.
Fertavid cartridges are not designed to allow any other drug to be mixed in the cartridges.
Discard used needles immediately after injection.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER

EU/1/09/510/017
9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 19 March 2009
Date of last renewal:

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

Fertavid 600 IU/0.72 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear and colourless solution.
In cartridges, designed to be used in conjunction with a pen injector.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In the female:
Fertavid 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 clomifene citrate.
• Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs [e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)].

In the male:
• Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

4.2 Posology and method of administration

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

Posology

Dosage in the female
There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasonography and monitoring of oestradiol levels.
When using the pen injector, it should be realised that the pen is a precision device which accurately delivers the dose to which it is set. It was shown that on average an 18% higher amount of FSH is given with the pen compared with a conventional syringe. This may be of particular relevance when switching between the pen injector and a conventional syringe within one treatment cycle. Especially when switching from a syringe to the pen, small dose adjustments may be needed to prevent too high a dose being given.
Based on the results of comparative clinical studies, it is considered appropriate to give a lower dosage of Fertavid than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation. Clinical experience with Fertavid is based on up to three treatment cycles in both indications. Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

- **Anovulation**
  A sequential treatment scheme is recommended starting with daily administration of 50 IU Fertavid. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol levels of 40-100% is considered to be optimal. The daily dose is then maintained until pre-ovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/ml (1000-3000 pmol/l) are attained. Usually, 7 to 14 days of treatment is sufficient to reach this state. The administration of Fertavid is then discontinued and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

  If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased. Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided to prevent multiple gestations.

- Controlled ovarian hyperstimulation in medically assisted reproduction programs
  Various stimulation protocols are applied. A starting dose of 100-225 IU is recommended for at least the first four days. Thereafter, the dose may be adjusted individually, based upon ovarian response. In clinical studies it was shown that maintenance dosages ranging from 75-375 IU for six to twelve days are sufficient, although longer treatment may be necessary. Fertavid can be given either alone, or, to prevent premature luteinisation, in combination with a GnRH agonist or antagonist. When using a GnRH agonist, a higher total treatment dose of Fertavid may be required to achieve an adequate follicular response. Ovarian response is monitored by ultrasonography and measurement of plasma oestradiol levels. When ultrasonographic evaluation indicates the presence of at least three follicles of 16-20 mm, and there is evidence of a good oestradiol response (plasma levels of about 300-400 picograms/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.

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

There is no relevant indication for use of Fertavid in children.

**Method of administration**

Fertavid solution for injection in cartridges has been developed for use in a pen injector called Puregon Pen and should be administered subcutaneously. The injection site should be alternated to prevent lipoatrophy.

Using the pen injector, injection of Fertavid can be carried out by the patient, provided that proper instructions are given by the physician.

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

4.4 Special warnings and 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. Appropriate FSH dose adjustment(s) should prevent multiple follicle development. Multiple gestation, especially high order, carries an increased risk of adverse maternal and perinatal outcomes. The patients should be advised of the potential risks of multiple births before starting treatment.
• The first injection of Fertavid should be performed under direct medical supervision.
• Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
• Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.
• The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g., maternal age, sperm characteristics) and multiple gestations.
• 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 Fertavid should be discontinued. In that case pregnancy should be avoided and hCG must be withheld, because it may induce, in addition to multiple ovulation, the ovarian hyperstimulation syndrome (OHSS). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with ovarian hyperstimulation syndrome. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.
• There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.
• Women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m2) or thrombophilia, may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotrophins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
• Fertavid may contain traces of streptomycin and/or neomycin. These antibiotics may cause hypersensitivity reactions in susceptible persons.
• Elevated endogeneous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to Fertavid/hCG therapy.
• In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

There is no indication for use of Fertavid during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotropins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Fertavid should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical use of Fertavid by the intramuscular or subcutaneous routes may lead to local reactions at the site of injection: bruising, pain, redness, swelling and itching are commonly reported (3% of all patients treated). The majority of these local reactions are mild and transient in nature. Generalised hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.1% of all patients treated with Fertavid).

Treatment of women:
In approximately 4% of the women treated with Fertavid in clinical trials, signs and symptoms related to ovarian hyperstimulation syndrome (OHSS) have been reported (see section 4.4). Other undesirable effects related to this syndrome were observed in clinical studies. These include pelvic pain and/or congestion, abdominal pain and/or distension, breast complaints (breast tenderness, pain and/or engorgement), ovarian enlargement, and spontaneous abortion. They were all reported at an incidence of approximately 1% (pelvic pain and abdominal distension) or less.
A slightly increased risk of ectopic pregnancy and multiple gestations has been seen.
Other more general symptoms that have been reported include headache and nausea (in up to 1% of the women treated with Fertavid).
In rare instances, thromboembolism has been associated with Fertavid/hCG therapy as with other gonadotrophins.

Treatment of men:
Gynaecomastia and acne may occur occasionally during Fertavid/hCG therapy. These are known effects of hCG treatment. In one subject an epididymal cyst was observed.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: gonadotrophins; ATC code: G03G A06.

Fertavid 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. Fertavid can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore Fertavid 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 Fertavid is generally followed by administration of hCG to induce the final phase of follicle maturation, resumption of meiosis and rupture of the follicle.

In men deficient in FSH, Fertavid should be used concomitantly with hCG for at least four months to promote spermatogenesis.

5.2 Pharmacokinetic properties

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

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 Fertavid 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, Fertavid induced no toxicologically significant effects. Fertavid showed no mutagenic potential in the Ames test and in the in vitro chromosome aberration test with human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fertavid 600 IU/0.72 ml solution for injection contains:
sucrose
sodium citrate
L-methionine
polysorbate 20
benzyl alcohol
water for injections.
The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

6.2 Incompatibilities

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

6.3 Shelf-life

3 years.

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the cartridge in the outer carton.
For patient convenience, Fertavid may be stored at or below 25 ºC by the patient for a single period of not more than 3 months.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Do not use if the solution contains particles or if the solution is not clear.
Fertavid 600 IU/0.72 ml solution for injection is designed for use in conjunction with a pen injector called Puregon Pen. The instructions for using the pen must be followed carefully.
Air bubbles must be removed from the cartridge before injection (see instructions for using the pen).
Empty cartridges must not be refilled.
Fertavid cartridges are not designed to allow any other drug to be mixed in the cartridges.
Discard used needles immediately after injection.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER

EU/1/09/510/018
9. DATE OF FIRST AUTHORIZAION/RENEWAL OF AUTHORIZATION

Date of first authorisation: 19 March 2009
Date of last renewal:

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

Fertavid 900 IU/1.08 ml solution for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection.
Clear and colourless solution.
In cartridges, designed to be used in conjunction with a pen injector.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

*In the female:*
Fertavid 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 clomifene citrate.
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs [e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)].

*In the male:*
- Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

4.2 **Posology and method of administration**

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

*Posology*

*Dosage in the female*
There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotrophins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasonography and monitoring of oestradiol levels.

When using the pen injector, it should be realised that the pen is a precision device which accurately delivers the dose to which it is set. It was shown that on average an 18% higher amount of FSH is given with the pen compared with a conventional syringe. This may be of particular relevance when switching between the pen injector and a conventional syringe within one treatment cycle. Especially when switching from a syringe to the pen, small dose adjustments may be needed to prevent too high a dose being given.
Based on the results of comparative clinical studies, it is considered appropriate to give a lower dosage of Fertavid than generally used for urinary FSH, not only in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation.

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

- **Anovulation**
  A sequential treatment scheme is recommended starting with daily administration of 50 IU Fertavid. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol levels of 40-100% is considered to be optimal. The daily dose is then maintained until pre-ovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/ml (1000-3000 pmol/l) are attained. Usually, 7 to 14 days of treatment is sufficient to reach this state. The administration of Fertavid is then discontinued and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

  If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased.

  Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided to prevent multiple gestations.

- **Controlled ovarian hyperstimulation in medically assisted reproduction programs**
  Various stimulation protocols are applied. A starting dose of 100-225 IU is recommended for at least the first four days. Thereafter, the dose may be adjusted individually, based upon ovarian response. In clinical studies it was shown that maintenance dosages ranging from 75-375 IU for six to twelve days are sufficient, although longer treatment may be necessary.

  Fertavid can be given either alone, or, to prevent premature luteinisation, in combination with a GnRH agonist or antagonist. When using a GnRH agonist, a higher total treatment dose of Fertavid may be required to achieve an adequate follicular response.

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

**Dosage in the male**

Fertavid should be given at a dosage of 450 IU/week, preferably divided in 3 dosages of 150 IU, concomitantly with hCG. The treatment should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. If a patient has not responded after this period, the combination therapy may be continued; current clinical experience indicates that treatment for up to 18 months or longer may be necessary to achieve spermatogenesis.

There is no relevant indication for use of Fertavid in children.

**Method of administration**

Fertavid solution for injection in cartridges has been developed for use in a pen injector called Puregon Pen and should be administered subcutaneously. The injection site should be alternated to prevent lipoatrophy.

Using the pen injector, injection of Fertavid can be carried out by the patient, provided that proper instructions are given by the physician.

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

4.4 Special warnings and 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. Appropriate FSH dose adjustment(s) should prevent multiple follicle development. Multiple gestation, especially high order, carries an increased risk of adverse maternal and perinatal outcomes. The patients should be advised of the potential risks of multiple births before starting treatment.
• The first injection of Fertavid should be performed under direct medical supervision.
• Since infertile women undergoing assisted reproduction, and particularly IVF, often have tubal abnormalities the incidence of ectopic pregnancies might be increased. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
• Rates of pregnancy loss in women undergoing assisted reproduction techniques are higher than in the normal population.
• The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g., maternal age, sperm characteristics) and multiple gestations.
• 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 Fertavid should be discontinued. In that case pregnancy should be avoided and hCG must be withheld, because it may induce, in addition to multiple ovulation, the ovarian hyperstimulation syndrome (OHSS). Clinical symptoms and signs of mild ovarian hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and mild to moderate enlargement of ovaries and ovarian cysts. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with ovarian hyperstimulation syndrome. In rare cases severe ovarian hyperstimulation syndrome occurs, which may be life-threatening. This is characterised by large ovarian cysts (prone to rupture), ascites, often hydrothorax and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS.
• There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. It is not yet established whether or not treatment with gonadotrophins increases the baseline risk of these tumours in infertile women.
• Women with generally recognised risk factors for thrombosis, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m²) or thrombophilia, may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotrophins. In these women the benefits of IVF treatment need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
• Fertavid may contain traces of streptomycin and/or neomycin. These antibiotics may cause hypersensitivity reactions in susceptible persons.
• Elevated endogeneous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to Fertavid/hCG therapy.
• In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

There is no indication for use of Fertavid during pregnancy. No teratogenic risk has been reported, following controlled ovarian hyperstimulation, in clinical use with gonadotropins. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH. However, to date, no particular malformative effect has been reported. No teratogenic effect has been observed in animal studies.

Fertavid should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical use of Fertavid by the intramuscular or subcutaneous routes may lead to local reactions at the site of injection: bruising, pain, redness, swelling and itching are commonly reported (3% of all patients treated). The majority of these local reactions are mild and transient in nature. Generalised hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.1% of all patients treated with Fertavid).

_Treatment of women:_

In approximately 4% of the women treated with Fertavid in clinical trials, signs and symptoms related to ovarian hyperstimulation syndrome (OHSS) have been reported (see section 4.4). Other undesirable effects related to this syndrome were observed in clinical studies. These include pelvic pain and/or congestion, abdominal pain and/or distension, breast complaints (breast tenderness, pain and/or engorgement), ovarian enlargement, and spontaneous abortion. They were all reported at an incidence of approximately 1% (pelvic pain and abdominal distension) or less.

A slightly increased risk of ectopic pregnancy and multiple gestations has been seen. Other more general symptoms that have been reported include headache and nausea (in up to 1% of the women treated with Fertavid).

In rare instances, thromboembolism has been associated with Fertavid/hCG therapy as with other gonadotrophins.

_Treatment of men:_

Gynaecomastia and acne may occur occasionally during Fertavid/hCG therapy. These are known effects of hCG treatment. In one subject an epididymal cyst was observed.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: gonadotrophins; ATC code: G03G A06.

Fertavid 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. Fertavid can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore Fertavid 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 Fertavid is generally followed by administration of hCG to induce the final phase of follicle maturation, resumption of meiosis and rupture of the follicle.

In men deficient in FSH, Fertavid should be used concomitantly with hCG for at least four months to promote spermatogenesis.

5.2 Pharmacokinetic properties

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

The absolute bioavailability of subcutaneously administered Fertavid is approximately 77%.

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 Fertavid 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, Fertavid induced no toxicologically significant effects. Fertavid showed no mutagenic potential in the Ames test and in the in vitro chromosome aberration test with human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fertavid 900 IU/1.08 ml solution for injection contains:
sucrose
sodium citrate
L-methionine
polysorbate 20
benzyl alcohol
water for injections.
The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

6.2 Incompatibilities

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

6.3 Shelf-life

3 years.

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the cartridge in the outer carton.
For patient convenience, Fertavid may be stored at or below 25 ºC by the patient for a single period of not more than 3 months.

6.5 Nature and contents of container

1.08 ml of solution in 1.5 ml cartridge (type I glass) with a grey rubber piston and an aluminium crimp-cap with a rubber inlay.
Pack of 1 cartridge and 9 needles to be used with the Puregon Pen.
Cartridges contain a minimum of 1025 IU FSH activity in 1.230 ml aqueous solution, which is sufficient for a net total dose of 900 IU.

6.6 Special precautions for disposal and other handling

Do not use if the solution contains particles or if the solution is not clear.
Fertavid 900 IU/1.08 ml solution for injection is designed for use in conjunction with a pen injector called Puregon Pen. The instructions for using the pen must be followed carefully.
Air bubbles must be removed from the cartridge before injection (see instructions for using the pen).
Empty cartridges must not be refilled.
Fertavid cartridges are not designed to allow any other drug to be mixed in the cartridges.
Discard used needles immediately after injection.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER

EU/1/09/510/019
9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 19 March 2009
Date of last renewal:

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

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

Biosearch Ireland
National Cell & Tissue Culture Centre
Glasnevin
Dublin 9
Ireland

Name and address of the manufacturers responsible for batch release

Fertavid solution for injection in vials 50 IU/0.5 ml, 75 IU/0.5 ml, 100 IU/0.5 ml, 150 IU/0.5 ml, 200 IU/0.5 ml:

N.V. Organon
Kloosterstraat 6
Postbus 20
5340 BH Oss
The Netherlands

Organon (Ireland) LTD.,
P.O. Box 2857
Swords, Co. Dublin
Ireland

SP,
Usine Saint Charles
60590 Eragny sur Epte
France.

Fertavid solution for injection in cartridges 150 IU/0.18 ml, 300 IU/0.36 ml, 600 IU/0.72 ml, 900 IU/1.08 ml:

N.V. Organon
Kloosterstraat 6
Postbus 20
5340 BH Oss
The Netherlands

Organon (Ireland) LTD.
P.O. Box 2857
Swords, Co. Dublin
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.
B. CONDITIONS OF THE MARKETING AUTHORISATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

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

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

Not applicable.

- OTHER CONDITIONS

*Pharmacovigilance system*

The MAH must ensure that the system of pharmacovigilance, as described in version 7.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

*PSURs*

The PSUR cycle of Fertavid will correspond to the one attributed to the cross-referred product, Puregon, until otherwise specified.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
1. NAME OF THE MEDICINAL PRODUCT

Fertavid 50 IU/0.5 ml solution for injection
follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follitropin beta corresponding to:
50 IU (100 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial containing 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vial in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/001

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**OUTER CARTON TEXT** Fertavid 50 IU/0.5 ml 5 vials

### 1. NAME OF THE MEDICINAL PRODUCT

Fertavid 50 IU/0.5 ml solution for injection follitropin beta

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follitropin beta corresponding to:
50 IU (100 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

### 3. LIST OF EXCIPIENTS

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

### 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
5 vials each containing 0.5 ml

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP:

### 9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vials in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/002

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
1. **NAME OF THE MEDICINAL PRODUCT**

Fertavid 50 IU/0.5 ml solution for injection
follitropin beta

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

1 vial contains 0.5 ml follitropin beta corresponding to:
50 IU (100 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

3. **LIST OF EXCIPIENTS**

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

4. **PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection
10 vials each containing 0.5 ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vials in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/003

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL TEXT Fertavid 50 IU/0.5 ml

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

Fertavid 50 IU/0.5 ml solution for injection
follitropin beta
Intramuscular and subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

BN:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

SP Europe
### 1. NAME OF THE MEDICINAL PRODUCT

Fertavid 75 IU/0.5 ml solution for injection
follitropin beta

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follitropin beta corresponding to:
75 IU (150 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

### 3. LIST OF EXCIPIENTS

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

### 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial containing 0.5 ml

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP:

### 9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months. Keep the vial in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/004

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
1. NAME OF THE MEDICINAL PRODUCT

Fertavid 75 IU/0.5 ml solution for injection
follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follitropin beta corresponding to:
75 IU (150 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
5 vials each containing 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vials in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/005

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT Fertavid 75 IU/0.5 ml 10 vials

1. NAME OF THE MEDICINAL PRODUCT

Fertavid 75 IU/0.5 ml solution for injection
follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follitropin beta corresponding to:
75 IU (150 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
10 vials each containing 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vials in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/006

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

VIAL TEXT Fertavid 75 IU/0.5 ml

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Fertavid 75 IU/0.5 ml solution for injection</td>
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<tr>
<td>follitropin beta</td>
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<tr>
<td>Intramuscular and subcutaneous use</td>
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</tbody>
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<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<th>3. EXPIRY DATE</th>
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<td>EXP:</td>
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<th>4. BATCH NUMBER</th>
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<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<th>6. OTHER</th>
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<tbody>
<tr>
<td>SP Europe</td>
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</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT Fertavid 100 IU/0.5 ml 1 vial

1. NAME OF THE MEDICINAL PRODUCT

Fertavid 100 IU/0.5 ml solution for injection
follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follitropin beta corresponding to:
100 IU (200 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial containing 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

79
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vial in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/007

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**OUTER CARTON TEXT** Fertavid 100 IU/0.5 ml 5 vials

---

1. **NAME OF THE MEDICINAL PRODUCT**

Fertavid 100 IU/0.5 ml solution for injection
follitropin beta

---

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

1 vial contains 0.5 ml follitropin beta corresponding to:
100 IU (200 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

---

3. **LIST OF EXCIPIENTS**

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

---

4. **PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection
5 vials each containing 0.5 ml

---

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

---

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

Keep out of the reach and sight of children.

---

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

---

8. **EXPIRY DATE**

EXP:

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9. **SPECIAL STORAGE CONDITIONS**
Store in a refrigerator. Do not freeze. The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months. Keep the vials in the outer carton.

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

### 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe  
Rue de Stalle 73  
B-1180 Bruxelles, Belgium

### 12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/008

### 13. BATCH NUMBER

BN:

### 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT Fertavid 100 IU/0.5 ml 10 vials

1. NAME OF THE MEDICINAL PRODUCT

Fertavid 100 IU/0.5 ml solution for injection follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follitropin beta corresponding to: 100 IU (200 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection 10 vials each containing 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use The contents of the vial should be used immediately after piercing of the rubber stopper. For single use only. Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator. Do not freeze. The patient may store Fertavid at or below 25°C for a single period of not more than 3 months. Keep the vials in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/009

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL TEXT Fertavid 100 IU/0.5 ml

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

Fertavid 100 IU/0.5 ml solution for injection
follitropin beta
Intramuscular and subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

BN:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

SP Europe
1. NAME OF THE MEDICINAL PRODUCT

Fertavid 150 IU/0.5 ml solution for injection follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follitropin beta corresponding to:
150 IU (300 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial containing 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vial in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/010

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON TEXT** Fertavid 150 IU/0.5 ml 5 vials

---

1. **NAME OF THE MEDICINAL PRODUCT**

   Fertavid 150 IU/0.5 ml solution for injection
   follitropin beta

---

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   1 vial contains 0.5 ml follitropin beta corresponding to:
   150 IU (300 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

---

3. **LIST OF EXCIPIENTS**

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

---

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Solution for injection
   5 vials each containing 0.5 ml

---

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Intramuscular and subcutaneous use
   The contents of the vial should be used immediately after piercing of the rubber stopper.
   For single use only.
   Read the package leaflet before use.

---

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

   Keep out of the reach and sight of children.

---

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

---

8. **EXPIRY DATE**

   EXP:

---

9. **SPECIAL STORAGE CONDITIONS**
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vials in the outer carton.

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

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

   SP Europe  
   Rue de Stalle 73  
   B-1180 Bruxelles, Belgium

12. **MARKETING AUTHORISATION NUMBER**

   EU/1/09/510/011

13. **BATCH NUMBER**

   BN:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**
1. NAME OF THE MEDICINAL PRODUCT

Fertavid 150 IU/0.5 ml solution for injection
follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follitropin beta corresponding to:
150 IU (300 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
10 vials each containing 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vials in the outer carton.

<table>
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<tr>
<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
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Rue de Stalle 73  
B-1180 Bruxelles, Belgium |
| 12. MARKETING AUTHORISATION NUMBER |
| EU/1/09/510/012 |
| 13. BATCH NUMBER |
| BN: |
| 14. GENERAL CLASSIFICATION FOR SUPPLY |
| Medicinal product subject to medical prescription. |
| 15. INSTRUCTIONS ON USE |
| 16. INFORMATION IN BRAILLE |
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL TEXT Fertavid 150 IU/0.5 ml

<table>
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<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Fertavid 150 IU/0.5 ml solution for injection</td>
</tr>
<tr>
<td>follitropin beta</td>
</tr>
<tr>
<td>Intramuscular and subcutaneous use</td>
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| 2. METHOD OF ADMINISTRATION                          |
|                                                     |

| 3. EXPIRY DATE                                       |
|                                                   |
| EXP:                                               |

| 4. BATCH NUMBER                                     |
|                                                   |
| BN:                                                |

| 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT         |
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| 6. OTHER                                           |
|                                                   |
| SP Europe                                          |
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT Fertavid 200 IU/0.5 ml 1 vial

1. NAME OF THE MEDICINAL PRODUCT

Fertavid 200 IU/0.5 ml solution for injection follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follitropin beta corresponding to:
200 IU (400 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial containing 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vial in the outer carton.

<table>
<thead>
<tr>
<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
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| SP Europe  
Rue de Stalle 73  
B-1180 Bruxelles, Belgium |

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<td>Medicinal product subject to medical prescription.</td>
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<tr>
<th>15. INSTRUCTIONS ON USE</th>
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<tr>
<th>16. INFORMATION IN BRAILLE</th>
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</thead>
</table>
### 1. NAME OF THE MEDICINAL PRODUCT

Fertavid 200 IU/0.5 ml solution for injection follicitropin beta

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follicitropin beta corresponding to:
200 IU (400 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

### 3. LIST OF EXCIPIENTS

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

### 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
5 vials each containing 0.5 ml

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP:

### 9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vials in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/014

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
1. NAME OF THE MEDICINAL PRODUCT

Fertavid 200 IU/0.5 ml solution for injection follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 0.5 ml follitropin beta corresponding to:
200 IU (400 IU/ml) recombinant follicle-stimulating hormone (FSH) activity.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
10 vials each containing 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular and subcutaneous use
The contents of the vial should be used immediately after piercing of the rubber stopper.
For single use only.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the vials in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/015

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL TEXT Fertavid 200 IU/0.5 ml

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

Fertavid 200 IU/0.5 ml solution for injection
follitropin beta
Intramuscular and subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

BN:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

SP Europe
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT Fertavid 150 IU/0.18 ml 1 cartridge

1. NAME OF THE MEDICINAL PRODUCT

Fertavid 150 IU/0.18 ml solution for injection follitropin beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

225 IU recombinant FSH activity/0.270 ml
Net content 150 IU

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 cartridge
1 pack with 3 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
For use only with a pen injector called Puregon Pen.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

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

Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the cartridge in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/016

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**CARTRIDGE TEXT** Fertavid 150 IU/0.18 ml

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertavid 150 IU/0.18 ml solution for injection</td>
</tr>
<tr>
<td>follitropin beta</td>
</tr>
<tr>
<td>Subcutaneous use</td>
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<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<th>3. EXPIRY DATE</th>
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<td>EXP:</td>
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<th>4. BATCH NUMBER</th>
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<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<tr>
<td>0.270 ml</td>
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<th>6. OTHER</th>
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<tbody>
<tr>
<td>SP Europe</td>
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</table>
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**OUTER CARTON TEXT** Fertavid 300 IU/0.36 ml 1 cartridge

### 1. NAME OF THE MEDICINAL PRODUCT

Fertavid 300 IU/0.36 ml solution for injection
follitropin beta

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

### 3. LIST OF EXCIPIENTS

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

### 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 cartridge
2 packs with 3 needles

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
For use only with a pen injector called Puregon Pen.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP:
Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days.
9. **SPECIAL STORAGE CONDITIONS**

Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the cartridge in the outer carton.

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

11. **NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER**

SP Europe  
Rue de Stalle 73  
B-1180 Bruxelles, Belgium

12. **MARKETING AUTHORIZATION NUMBER**

EU/1/09/510/017

13. **BATCH NUMBER**

BN:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**
**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**CARTRIDGE TEXT Fertavid 300 IU/0.36 ml**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Fertavid 300 IU/0.36 ml solution for injection</td>
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<tr>
<td>follitropin beta</td>
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<tr>
<td>Subcutaneous use</td>
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<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<th>3. EXPIRY DATE</th>
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<th>4. BATCH NUMBER</th>
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<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<tr>
<td>0.480 ml</td>
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<tr>
<th>6. OTHER</th>
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<tbody>
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<td>SP Europe</td>
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</table>
1. **NAME OF THE MEDICINAL PRODUCT**

Fertavid 600 IU/0.72 ml solution for injection
follitropin beta

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

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

3. **LIST OF EXCIPIENTS**

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

4. **PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection
1 cartridge
2 packs with 3 needles

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use
For use only with a pen injector called Puregon Pen.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

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

Store in a refrigerator. Do not freeze.
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months.
Keep the cartridge in the outer carton.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORITY

SP Europe
Rue de Stalle 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORIZATION NUMBER

EU/1/09/510/018

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**CARTRIDGE TEXT Fertavid 600 IU/0.72 ml**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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</thead>
<tbody>
<tr>
<td>Fertavid 600 IU/0.72 ml solution for injection</td>
</tr>
<tr>
<td>follitropin beta</td>
</tr>
<tr>
<td>Subcutaneous use</td>
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<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<tr>
<th>3. EXPIRY DATE</th>
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<td>EXP:</td>
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<th>4. BATCH NUMBER</th>
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<td>BN:</td>
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<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<tbody>
<tr>
<td>0.840 ml</td>
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<tr>
<th>6. OTHER</th>
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</thead>
<tbody>
<tr>
<td>SP Europe</td>
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<tr>
<td>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</td>
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<tr>
<td>--------------------------------------------</td>
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<tr>
<td>OUTER CARTON TEXT Fertavid 900 IU/1.08 ml 1 cartridge</td>
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<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tr>
<td>Fertavid 900 IU/1.08 ml solution for injection follitropin beta</td>
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<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
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<tbody>
<tr>
<td>1025 IU recombinant FSH activity/1.230 ml Net content 900 IU</td>
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<tr>
<th>3. LIST OF EXCIPIENTS</th>
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<tbody>
<tr>
<td>Other ingredients: sucrose, sodium citrate, L-methionine, polysorbate 20 and benzyl alcohol in water for injections; sodium hydroxide and/or hydrochloric acid as pH adjustment.</td>
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<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
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<tbody>
<tr>
<td>Solution for injection 1 cartridge 3 packs with 3 needles</td>
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</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
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<tbody>
<tr>
<td>Subcutaneous use For use only with a pen injector called Puregon Pen. Read the package leaflet before use.</td>
</tr>
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<table>
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<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
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<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
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<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<tr>
<th>8. EXPIRY DATE</th>
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<tbody>
<tr>
<td>EXP: Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days.</td>
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</tbody>
</table>
### 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. 
The patient may store Fertavid at or below 25 °C for a single period of not more than 3 months. 
Keep the cartridge in the outer carton.

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

### 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe  
Rue de Stalle 73  
B-1180 Bruxelles, Belgium

### 12. MARKETING AUTHORISATION NUMBER

EU/1/09/510/019

### 13. BATCH NUMBER

BN:

### 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE TEXT Fertavid 900 IU/1.08 ml

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Fertavid 900 IU/1.08 ml solution for injection</td>
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<tr>
<td>follitropin beta</td>
</tr>
<tr>
<td>Subcutaneous use</td>
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<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<th>3. EXPIRY DATE</th>
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<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<tr>
<td>1.230 ml</td>
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<th>6. OTHER</th>
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<tr>
<td>SP Europe</td>
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</table>
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Fertavid is and what it is used for
2. Before you use Fertavid
3. How to use Fertavid
4. Possible side effects
5. How to store Fertavid
6. Further information

1. WHAT FERTAVID IS AND WHAT IT IS USED FOR

Fertavid solution for injection contains follitropin beta, a hormone known as follicle-stimulating hormone (FSH). FSH belongs to the group of gonadotrophins, which play an important role in human fertility and reproduction. 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. In men, FSH is needed for the production of sperm.

Fertavid is used to treat infertility in any of the following situations:
- In women who are not ovulating, Fertavid can be used to cause ovulation in women who have not responded to treatment with clomifene citrate.
- In women undergoing assisted reproduction techniques, including in vitro fertilisation (IVF) and other methods, Fertavid can be used to bring about the development of multiple follicles.
- In men who are infertile due to a hormonal deficiency, Fertavid can be used for the production of sperm.

2. BEFORE YOU USE FERTAVID

Do not use Fertavid
- if you have a tumour of the ovary, breast, uterus, testis, pituitary gland or hypothalamus
- if you are allergic (hypersensitive) to follitropin beta or any of the other ingredients of Fertavid
- if you have heavy or irregular vaginal bleeding where the cause is not known
- if you suffer from primary ovarian failure
- if you have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD)
- if you have malformations of the sexual organs which make a normal pregnancy impossible
- if you have fibroids in the uterus which make a normal pregnancy impossible
- if you suffer from primary testicular failure.

Take special care with Fertavid
Please inform your doctor if you have experienced an allergic reaction to neomycin and/or streptomycin (antibiotics) in the past.

If you are a woman:
Close supervision by your 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 your doctor to choose the correct dose of Fertavid 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 your 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.

Treatment with Fertavid (like pregnancy itself) may increase the risk of thrombosis (the formation of a blood clot in a blood vessel, most often in the veins of the legs or the lungs). Please discuss this with your doctor, before starting treatment, especially if:
• you already know you have an increased risk of thrombosis
• you, or anyone in your immediate family, have ever had a thrombosis
• you are severely overweight.

If you are a man:
Elevated FSH blood levels are indicative of testicular damage. Fertavid is usually not effective in such cases. To monitor treatment, your doctor may ask you for a semen analysis to be performed 4 to 6 months after the beginning of treatment.

Using other medicines

If Fertavid is used in combination with clomifene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Fertavid may be needed to achieve a response. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy

There is neither clinical experience nor evidence from studies in animals that use of Fertavid during pregnancy might lead to congenital abnormalities. Nevertheless, you should not use Fertavid if you are already pregnant, or suspect that you might be pregnant.
After treatment with gonadotrophin preparations, there is an increased risk of having multiple pregnancies. Multiple pregnancies carry an increased health risk for both the mother and her babies around the time of birth. Furthermore, multiple pregnancies and characteristics of the patients undergoing fertility treatment (e.g. age of the female, sperm characteristics) may be associated with an increased risk of congenital abnormalities. There is a slightly increased risk of extra-uterine pregnancy in women with damaged fallopian tubes.
In women undergoing fertility treatment there may be a slightly higher risk of miscarriage.

Breast-feeding

You should not use Fertavid if you are breast-feeding.

Driving and using machines

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

3. HOW TO USE FERTAVID
Always use Fertavid exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Dosage in women**

Your doctor will decide on the dose of Fertavid to be given. This dose may be adjusted as your treatment progresses. Further details on the treatment schedule are given below.

There are large differences between women in the response of the ovaries to FSH, which makes it impossible to set a dosage schedule which is suitable for all patients. To find the right dosage, follicle growth is checked by means of ultrasound scanning, and measurement of the amount of estradiol (female sex hormone) in blood or urine.

- **Women who are not ovulating**
  Initially, a starting dose is set by your doctor. This dose is continued for at least seven days. If there is no ovarian response, the daily dose will then be gradually increased until follicle growth and/or plasma 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 Fertavid is then stopped and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

- **Medically assisted reproduction programs, e.g. IVF**
  A starting dose is set by your doctor. This dose is continued for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their ovarian response. 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.

**Dosage in men**

Fertavid is usually prescribed at a dose of 450 IU/week, mostly in 3 dosages of 150 IU, in combination with another hormone (hCG), for at least 3 to 4 months. If you have not responded after this period, your treatment may carry on for at least 18 months.

**Method and route of administration**

Fertavid only works if it is injected in a muscle or under the skin. The very first injection of Fertavid should be given under medical supervision. 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 (intramuscular) should only be given by a doctor or a nurse. Injections under the skin (subcutaneous) may, in some cases, be given by you or your partner. Your doctor will tell you when and how to do this. When the instructions are followed carefully, Fertavid will be administered properly and with minimal discomfort.

**Instructions for use**

*Step 1 - Preparing the syringe*

Sterile disposable syringes and needles should be used for administration of Fertavid. The volume of the syringe should be small enough so that the prescribed dose can be given with reasonable accuracy. Fertavid solution for injection comes in a glass vial. Do not use if the solution contains particles or is not clear. First, remove the flip-off cap of the vial. Place a needle on a syringe and pierce the needle through the rubber stopper of the vial (a). Draw the solution up into the syringe (b), and replace the needle with an injection needle (c). Finally hold the syringe with the needle pointing upwards and gently tap the side to force any air bubbles up to the top; then squeeze the plunger until all the air has been expelled, and only Fertavid solution is left in the syringe (d). If necessary, the plunger may be squeezed further, to adjust the volume to be administered.
**Step 2 - The injection site**
The best site for subcutaneous injection is in the abdomen around the navel (e) where there is a lot of loose skin and layers of fatty tissue. You should vary the injection site a little with each injection. It is possible to inject in other areas. Your doctor or nurse will advise you where to inject.

**Step 3 - Preparing the area**
A few taps at the injection site will stimulate tiny nerve endings and help reduce discomfort when the needle goes in. Hands should be washed and the injection site swabbed with disinfectant (for example chlorohexidine 0.5%) to remove any surface bacteria. Clean about two inches around the point where the needle will go in and let the disinfectant dry for at least one minute before proceeding.

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

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

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

**Step 7 - Removing the syringe**
Pull the syringe out quickly and apply pressure to the injection site with a swab containing disinfectant. A gentle massage of the site - while still maintaining pressure - helps disperse the Fertavid solution and relieve any discomfort.

Any remaining solution should be discarded.
Do not mix Fertavid with any other medicines.

**If you use more Fertavid than you should**
Inform your doctor.
Too high a dose may cause overstimulation of the ovaries. See section on Possible side effects below.

**If you forget to use Fertavid**
Do not take a double dose to make up for a forgotten dose.
Do tell your doctor that you missed a dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fertavid can cause side effects, although not everybody gets them.
Minor side effects include bruising, pain, redness, swelling and itching at the site of the injection.
Occasionally, more widespread reactions like rash have been observed.

*If you are a woman:*
A complication with FSH treatment is unwanted overstimulation of the ovaries. This condition can become very serious, but 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.
Rarely, blood clots may occur without unwanted overstimulation of the ovaries (see also “Take special care with Fertavid”).

Other side effects observed in clinical studies include headache and nausea.

*If you are a man:*
Some breast development or acne may occur due to treatment with hCG.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FERTAVID

Keep out of the reach and sight of children.

Do not use Fertavid after the expiry date which is stated on the label after 'EXP:'.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial(s) in the outer carton.

For your convenience, you may store Fertavid at or below 25 °C (at room temperature) for a single period of not more than 3 months.
Make a note of when you start storing the product out of the refrigerator.

The contents of a vial should be used immediately after piercing the rubber stopper.
Do not use Fertavid if you notice that the solution contains particles or is not clear.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Fertavid contains
• The active substance is follitropin beta, a hormone known as follicle-stimulating hormone (FSH) in a strength of 50 IU in 0.5 ml aqueous solution per vial.
• The other ingredients are sucrose, sodium citrate, L-methionine and polysorbate 20 in water for injections. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

What Fertavid looks like and contents of the pack

Fertavid solution for injection is a clear, colourless solution. It is supplied in a glass vial. It is available in packs of 1, 5 or 10 vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
SP Europe, Rue de Stalle 73, B-1180 Bruxelles, Belgium.

Manufacturer
• N.V. Organon, Kloosterstraat 6, Postbus 20, 5340 BH Oss, The Netherlands
• Organon (Ireland) Ltd., P.O. Box 2857, Drynam Road, Swords, Co. Dublin, Ireland
• SP, Usine Saint Charles, 60590 Eragny sur Epte, France

This leaflet was last approved in

In correspondence please quote the batch number.
Fertavid 75 IU/0.5 ml solution for injection
follitropin beta

Read all of this leaflet carefully before you start using this medicine.
− Keep this leaflet. You may need to read it again.
− If you have any further questions, ask your doctor or pharmacist.
− This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
− If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Fertavid is and what it is used for
2. Before you use Fertavid
3. How to use Fertavid
4. Possible side effects
5. How to store Fertavid
6. Further information

1. WHAT FERTAVID IS AND WHAT IT IS USED FOR

Fertavid solution for injection contains follitropin beta, a hormone known as follicle-stimulating hormone (FSH).
FSH belongs to the group of gonadotrophins, which play an important role in human fertility and reproduction. 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. In men, FSH is needed for the production of sperm.

Fertavid is used to treat infertility in any of the following situations:
• In women who are not ovulating, Fertavid can be used to cause ovulation in women who have not responded to treatment with clomifene citrate.
• In women undergoing assisted reproduction techniques, including in vitro fertilisation (IVF) and other methods, Fertavid can be used to bring about the development of multiple follicles.
• In men who are infertile due to a hormonal deficiency, Fertavid can be used for the production of sperm.

2. BEFORE YOU USE FERTAVID

Do not use Fertavid

• if you have a tumour of the ovary, breast, uterus, testis, pituitary gland or hypothalamus
• if you are allergic (hypersensitive) to follitropin beta or any of the other ingredients of Fertavid
• if you have heavy or irregular vaginal bleeding where the cause is not known
• if you suffer from primary ovarian failure
• if you have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD)
• if you have malformations of the sexual organs which make a normal pregnancy impossible
• if you have fibroids in the uterus which make a normal pregnancy impossible
• if you suffer from primary testicular failure.

Take special care with Fertavid
Please inform your doctor if you have experienced an allergic reaction to neomycin and/or streptomycin (antibiotics) in the past.

If you are a woman:
Close supervision by your 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 your doctor to choose the correct dose of Fertavid 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 your 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.

Treatment with Fertavid (like pregnancy itself) may increase the risk of thrombosis (the formation of a blood clot in a blood vessel, most often in the veins of the legs or the lungs). Please discuss this with your doctor, before starting treatment, especially if:
• you already know you have an increased risk of thrombosis
• you, or anyone in your immediate family, have ever had a thrombosis
• you are severely overweight.

If you are a man:
Elevated FSH blood levels are indicative of testicular damage. Fertavid is usually not effective in such cases. To monitor treatment, your doctor may ask you for a semen analysis to be performed 4 to 6 months after the beginning of treatment.

Using other medicines
If Fertavid is used in combination with clomifene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Fertavid may be needed to achieve a response. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy
There is neither clinical experience nor evidence from studies in animals that use of Fertavid during pregnancy might lead to congenital abnormalities. Nevertheless, you should not use Fertavid if you are already pregnant, or suspect that you might be pregnant.

After treatment with gonadotrophin preparations, there is an increased risk of having multiple pregnancies. Multiple pregnancies carry an increased health risk for both the mother and her babies around the time of birth. Furthermore, multiple pregnancies and characteristics of the patients undergoing fertility treatment (e.g. age of the female, sperm characteristics) may be associated with an increased risk of congenital abnormalities. There is a slightly increased risk of extra-uterine pregnancy in women with damaged fallopian tubes.

In women undergoing fertility treatment there may be a slightly higher risk of miscarriage.

Breast feeding
You should not use Fertavid if you are breast-feeding.

Driving and using machines
No effects on the ability to drive and use machines have been observed.

3. HOW TO USE FERTAVID
Always use Fertavid exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Dosage in women**

Your doctor will decide on the dose of Fertavid to be given. This dose may be adjusted as your treatment progresses. Further details on the treatment schedule are given below.

There are large differences between women in the response of the ovaries to FSH, which makes it impossible to set a dosage schedule which is suitable for all patients. To find the right dosage, follicle growth is checked by means of ultrasound scanning, and measurement of the amount of estradiol (female sex hormone) in blood or urine.

- **Women who are not ovulating**
  Initially, a starting dose is set by your doctor. This dose is continued for at least seven days. If there is no ovarian response, the daily dose will then be gradually increased until follicle growth and/or plasma 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 Fertavid is then stopped and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

- **Medically assisted reproduction programs, e.g. IVF**
  A starting dose is set by your doctor. This dose is continued for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their ovarian response. 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.

**Dosage in men**

Fertavid is usually prescribed at a dose of 450 IU/week, mostly in 3 dosages of 150 IU, in combination with another hormone (hCG), for at least 3 to 4 months. If you have not responded after this period, your treatment may carry on for at least 18 months.

**Method and route of administration**

Fertavid only works if it is injected in a muscle or under the skin. The very first injection of Fertavid should be given under medical supervision. 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 (intramuscular) should only be given by a doctor or a nurse. Injections under the skin (subcutaneous) may, in some cases, be given by you or your partner. Your doctor will tell you when and how to do this. When the instructions are followed carefully, Fertavid will be administered properly and with minimal discomfort.

**Instructions for use**

**Step 1 - Preparing the syringe**
Sterile disposable syringes and needles should be used for administration of Fertavid. The volume of the syringe should be small enough so that the prescribed dose can be given with reasonable accuracy. Fertavid solution for injection comes in a glass vial. Do not use if the solution contains particles or is not clear. First, remove the flip-off cap of the vial. Place a needle on a syringe and pierce the needle through the rubber stopper of the vial (a). Draw the solution up into the syringe (b), and replace the needle with an injection needle (c). Finally hold the syringe with the needle pointing upwards and gently tap the side to force any air bubbles up to the top; then squeeze the plunger until all the air has been expelled, and only Fertavid solution is left in the syringe (d). If necessary, the plunger may be squeezed further, to adjust the volume to be administered.
Step 2 - The injection site
The best site for subcutaneous injection is in the abdomen around the navel (e) where there is a lot of loose skin and layers of fatty tissue. You should vary the injection site a little with each injection. It is possible to inject in other areas. Your doctor or nurse will advise you where to inject.

Step 3 - Preparing the area
A few taps at the injection site will stimulate tiny nerve endings and help reduce discomfort when the needle goes in. Hands should be washed and the injection site swabbed with disinfectant (for example chlorohexidine 0.5%) to remove any surface bacteria. Clean about two inches around the point where the needle will go in and let the disinfectant dry for at least one minute before proceeding.

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

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

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

Step 7 - Removing the syringe
Pull the syringe out quickly and apply pressure to the injection site with a swab containing disinfectant. A gentle massage of the site - while still maintaining pressure - helps disperse the Fertavid solution and relieve any discomfort.

Any remaining solution should be discarded.
Do not mix Fertavid with any other medicines.

**If you use more Fertavid than you should**
Inform your doctor.
Too high a dose may cause overstimulation of the ovaries. See section on Possible side effects below.
If you forget to use Fertavid

Do not take a double dose to make up for a forgotten dose.
Do tell your doctor that you missed a dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fertavid can cause side effects, although not everybody gets them.
Minor side effects include bruising, pain, redness, swelling and itching at the site of the injection.
Occasionally, more widespread reactions like rash have been observed.

If you are a woman:
A complication with FSH treatment is unwanted overstimulation of the ovaries. This condition can become very serious, but 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.
Rarely, blood clots may occur without unwanted overstimulation of the ovaries (see also “Take special care with Fertavid”).

Other side effects observed in clinical studies include headache and nausea.

If you are a man:
Some breast development or acne may occur due to treatment with hCG.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FERTAVID

Keep out of the reach and sight of children.

Do not use Fertavid after the expiry date which is stated on the label after 'EXP:'.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial(s) in the outer carton.

For your convenience, you may store Fertavid at or below 25 °C (at room temperature) for a single period of not more than 3 months.
Make a note of when you start storing the product out of the refrigerator.

The contents of a vial should be used immediately after piercing the rubber stopper.
Do not use Fertavid if you notice that the solution contains particles or is not clear.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Fertavid contains
• The active substance is follitropin beta, a hormone known as follicle-stimulating hormone (FSH) in a strength of 75 IU in 0.5 ml aqueous solution per vial.
• The other ingredients are sucrose, sodium citrate, L-methionine and polysorbate 20 in water for injections. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

What Fertavid looks like and contents of the pack

Fertavid solution for injection is a clear, colourless solution. It is supplied in a glass vial. It is available in packs of 1, 5 or 10 vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
SP Europe, Rue de Stalle 73, B-1180 Bruxelles, Belgium.

Manufacturer
• N.V. Organon, Kloosterstraat 6, Postbus 20, 5340 BH Oss, The Netherlands
• Organon (Ireland) Ltd., P.O. Box 2857, Drynam Road, Swords, Co. Dublin, Ireland
• SP, Usine Saint Charles, 60590 Eragny sur Epte, France

This leaflet was last approved in

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1. WHAT FERTAVID IS AND WHAT IT IS USED FOR

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

FSH belongs to the group of gonadotrophins, which play an important role in human fertility and reproduction. 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. In men, FSH is needed for the production of sperm.

Fertavid is used to treat infertility in any of the following situations:

- In women who are not ovulating, Fertavid can be used to cause ovulation in women who have not responded to treatment with clomifene citrate.
- In women undergoing assisted reproduction techniques, including in vitro fertilisation (IVF) and other methods, Fertavid can be used to bring about the development of multiple follicles.
- In men who are infertile due to a hormonal deficiency, Fertavid can be used for the production of sperm.

2. BEFORE YOU USE FERTAVID

Do not use Fertavid

- if you have a tumour of the ovary, breast, uterus, testis, pituitary gland or hypothalamus
- if you are allergic (hypersensitive) to follitropin beta or any of the other ingredients of Fertavid
- if you have heavy or irregular vaginal bleeding where the cause is not known
- if you suffer from primary ovarian failure
- if you have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD)
- if you have malformations of the sexual organs which make a normal pregnancy impossible
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Take special care with Fertavid
Please inform your doctor if you have experienced an allergic reaction to neomycin and/or streptomycin (antibiotics) in the past.

If you are a woman:
Close supervision by your 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 your doctor to choose the correct dose of Fertavid 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 your 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.

Treatment with Fertavid (like pregnancy itself) may increase the risk of thrombosis (the formation of a blood clot in a blood vessel, most often in the veins of the legs or the lungs). Please discuss this with your doctor, before starting treatment, especially if:
- you already know you have an increased risk of thrombosis
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- you are severely overweight.

If you are a man:
Elevated FSH blood levels are indicative of testicular damage. Fertavid is usually not effective in such cases. To monitor treatment, your doctor may ask you for a semen analysis to be performed 4 to 6 months after the beginning of treatment.

Using other medicines
If Fertavid is used in combination with clomifene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Fertavid may be needed to achieve a response. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy
There is neither clinical experience nor evidence from studies in animals that use of Fertavid during pregnancy might lead to congenital abnormalities. Nevertheless, you should not use Fertavid if you are already pregnant, or suspect that you might be pregnant.
After treatment with gonadotrophin preparations, there is an increased risk of having multiple pregnancies. Multiple pregnancies carry an increased health risk for both the mother and her babies around the time of birth. Furthermore, multiple pregnancies and characteristics of the patients undergoing fertility treatment (e.g. age of the female, sperm characteristics) may be associated with an increased risk of congenital abnormalities. There is a slightly increased risk of extra-uterine pregnancy in women with damaged fallopian tubes.
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Dosage in women

Your doctor will decide on the dose of Fertavid to be given. This dose may be adjusted as your treatment progresses. Further details on the treatment schedule are given below. There are large differences between women in the response of the ovaries to FSH, which makes it impossible to set a dosage schedule which is suitable for all patients. To find the right dosage, follicle growth is checked by means of ultrasound scanning, and measurement of the amount of estradiol (female sex hormone) in blood or urine.

- **Women who are not ovulating**
  Initially, a starting dose is set by your doctor. This dose is continued for at least seven days. If there is no ovarian response, the daily dose will then be gradually increased until follicle growth and/or plasma 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 Fertavid is then stopped and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

- **Medically assisted reproduction programs, e.g. IVF**
  A starting dose is set by your doctor. This dose is continued for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their ovarian response. 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.

Dosage in men

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Method and route of administration

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Instructions for use

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

Step 3 - Preparing the area
A few taps at the injection site will stimulate tiny nerve endings and help reduce discomfort when the needle goes in. Hands should be washed and the injection site swabbed with disinfectant (for example chlorohexidine 0.5%) to remove any surface bacteria. Clean about two inches around the point where the needle will go in and let the disinfectant dry for at least one minute before proceeding.

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

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

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Depress the plunger slowly and steadily, so the solution is correctly injected and the skin tissues are not damaged.

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Any remaining solution should be discarded.
Do not mix Fertavid with any other medicines.

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Inform your doctor.
Too high a dose may cause overstimulation of the ovaries. See section on Possible side effects below.
If you forget to use Fertavid

Do not take a double dose to make up for a forgotten dose.
Do tell your doctor that you missed a dose.

4. POSSIBLE SIDE EFFECTS

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Occasionally, more widespread reactions like rash have been observed.

If you are a woman:
A complication with FSH treatment is unwanted overstimulation of the ovaries. This condition can become very serious, but 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.
Rarely, blood clots may occur without unwanted overstimulation of the ovaries (see also “Take special care with Fertavid”).

Other side effects observed in clinical studies include headache and nausea.

If you are a man:
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For your convenience, you may store Fertavid at or below 25 °C (at room temperature) for a single period of not more than 3 months.
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Do not use Fertavid if you notice that the solution contains particles or is not clear.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Fertavid contains
• The active substance is follitropin beta, a hormone known as follicle-stimulating hormone (FSH) in a strength of 100 IU in 0.5 ml aqueous solution per vial.
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• SP, Usine Saint Charles, 60590 Eragny sur Epte, France

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- you, or anyone in your immediate family, have ever had a thrombosis
- you are severely overweight.

If you are a man:
Elevated FSH blood levels are indicative of testicular damage. Fertavid is usually not effective in such cases. To monitor treatment, your doctor may ask you for a semen analysis to be performed 4 to 6 months after the beginning of treatment.

Using other medicines

If Fertavid is used in combination with clomifene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Fertavid may be needed to achieve a response. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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In women undergoing fertility treatment there may be a slightly higher risk of miscarriage.

Breast-feeding

You should not use Fertavid if you are breast-feeding.

Driving and using machines

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

3. **HOW TO USE FERTAVID**
Always use Fertavid exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

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- **Medically assisted reproduction programs, e.g. IVF**
  A starting dose is set by your doctor. This dose is continued for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their ovarian response. 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.

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Fertavid is usually prescribed at a dose of 450 IU/week, mostly in 3 dosages of 150 IU, in combination with another hormone (hCG), for at least 3 to 4 months. If you have not responded after this period, your treatment may carry on for at least 18 months.

**Method and route of administration**

Fertavid only works if it is injected in a muscle or under the skin.

The very first injection of Fertavid should be given under medical supervision. 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 (intramuscular) should only be given by a doctor or a nurse.

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**Instructions for use**

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Sterile disposable syringes and needles should be used for administration of Fertavid. The volume of the syringe should be small enough so that the prescribed dose can be given with reasonable accuracy. Fertavid solution for injection comes in a glass vial. Do not use if the solution contains particles or is not clear. First, remove the flip-off cap of the vial. Place a needle on a syringe and pierce the needle through the rubber stopper of the vial (a). Draw the solution up into the syringe (b), and replace the needle with an injection needle (c). Finally hold the syringe with the needle pointing upwards and gently tap the side to force any air bubbles up to the top; then squeeze the plunger until all the air has been expelled, and only Fertavid solution is left in the syringe (d). If necessary, the plunger may be squeezed further, to adjust the volume to be administered.
Step 2 - The injection site
The best site for subcutaneous injection is in the abdomen around the navel (e) where there is a lot of loose skin and layers of fatty tissue. You should vary the injection site a little with each injection. It is possible to inject in other areas. Your doctor or nurse will advise you where to inject.

Step 3 - Preparing the area
A few taps at the injection site will stimulate tiny nerve endings and help reduce discomfort when the needle goes in. Hands should be washed and the injection site swabbed with disinfectant (for example chlorohexidine 0.5%) to remove any surface bacteria. Clean about two inches around the point where the needle will go in and let the disinfectant dry for at least one minute before proceeding.

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

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

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

Step 7 - Removing the syringe
Pull the syringe out quickly and apply pressure to the injection site with a swab containing disinfectant. A gentle massage of the site - while still maintaining pressure - helps disperse the Fertavid solution and relieve any discomfort.

Any remaining solution should be discarded.
Do not mix Fertavid with any other medicines.

If you use more Fertavid than you should
Inform your doctor.
Too high a dose may cause overstimulation of the ovaries. See section on Possible side effects below.
If you forget to use Fertavid

Do not take a double dose to make up for a forgotten dose.
Do tell your doctor that you missed a dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fertavid can cause side effects, although not everybody gets them.
Minor side effects include bruising, pain, redness, swelling and itching at the site of the injection.
Occasionally, more widespread reactions like rash have been observed.

If you are a woman:
A complication with FSH treatment is unwanted overstimulation of the ovaries. This condition can become very serious, but 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.
Rarely, blood clots may occur without unwanted overstimulation of the ovaries (see also “Take special care with Fertavid”).

Other side effects observed in clinical studies include headache and nausea.

If you are a man:
Some breast development or acne may occur due to treatment with hCG.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FERTAVID

Keep out of the reach and sight of children.

Do not use Fertavid after the expiry date which is stated on the label after 'EXP:'.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial(s) in the outer carton.

For your convenience, you may store Fertavid at or below 25 °C (at room temperature) for a single period of not more than 3 months.
Make a note of when you start storing the product out of the refrigerator.

The contents of a vial should be used immediately after piercing the rubber stopper.
Do not use Fertavid if you notice that the solution contains particles or is not clear.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Fertavid contains
The active substance is follitropin beta, a hormone known as follicle-stimulating hormone (FSH) in a strength of 150 IU in 0.5 ml aqueous solution per vial. The other ingredients are sucrose, sodium citrate, L-methionine and polysorbate 20 in water for injections. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

**What Fertavid looks like and contents of the pack**

Fertavid solution for injection is a clear, colourless solution. It is supplied in a glass vial. It is available in packs of 1, 5 or 10 vials. Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
SP Europe, Rue de Stalle 73, B-1180 Bruxelles, Belgium.

**Manufacturer**
- N.V. Organon, Kloosterstraat 6, Postbus 20, 5340 BH Oss, The Netherlands
- Organon (Ireland) Ltd., P.O. Box 2857, Drynam Road, Swords, Co. Dublin, Ireland
- SP, Usine Saint Charles, 60590 Eragny sur Epte, France

**This leaflet was last approved in**

In correspondence please quote the batch number.
Fertavid 200 IU/0.5 ml solution for injection
follitropin beta

In this leaflet:
1. What Fertavid is and what it is used for
2. Before you use Fertavid
3. How to use Fertavid
4. Possible side effects
5. How to store Fertavid
6. Further information

1. WHAT FERTAVID IS AND WHAT IT IS USED FOR

Fertavid solution for injection contains follitropin beta, a hormone known as follicle-stimulating hormone (FSH). FSH belongs to the group of gonadotrophins, which play an important role in human fertility and reproduction. 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. In men, FSH is needed for the production of sperm.

Fertavid is used to treat infertility in any of the following situations:
- In women who are not ovulating, Fertavid can be used to cause ovulation in women who have not responded to treatment with clomifene citrate.
- In women undergoing assisted reproduction techniques, including in vitro fertilisation (IVF) and other methods, Fertavid can be used to bring about the development of multiple follicles.
- In men who are infertile due to a hormonal deficiency, Fertavid can be used for the production of sperm.

2. BEFORE YOU USE FERTAVID

Do not use Fertavid
- if you have a tumour of the ovary, breast, uterus, testis, pituitary gland or hypothalamus
- if you are allergic (hypersensitive) to follitropin beta or any of the other ingredients of Fertavid
- if you have heavy or irregular vaginal bleeding where the cause is not known
- if you suffer from primary ovarian failure
- if you have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD)
- if you have malformations of the sexual organs which make a normal pregnancy impossible
- if you have fibroids in the uterus which make a normal pregnancy impossible
- if you suffer from primary testicular failure.

Take special care with Fertavid

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
Please inform your doctor if you have experienced an allergic reaction to neomycin and/or streptomycin (antibiotics) in the past.

If you are a woman:
Close supervision by your 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 your doctor to choose the correct dose of Fertavid 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 your 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.

Treatment with Fertavid (like pregnancy itself) may increase the risk of thrombosis (the formation of a blood clot in a blood vessel, most often in the veins of the legs or the lungs). Please discuss this with your doctor, before starting treatment, especially if:
- you already know you have an increased risk of thrombosis
- you, or anyone in your immediate family, have ever had a thrombosis
- you are severely overweight.

If you are a man:
Elevated FSH blood levels are indicative of testicular damage. Fertavid is usually not effective in such cases. To monitor treatment, your doctor may ask you for a semen analysis to be performed 4 to 6 months after the beginning of treatment.

Using other medicines

If Fertavid is used in combination with clomifene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Fertavid may be needed to achieve a response. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy

There is neither clinical experience nor evidence from studies in animals that use of Fertavid during pregnancy might lead to congenital abnormalities. Nevertheless, you should not use Fertavid if you are already pregnant, or suspect that you might be pregnant.

After treatment with gonadotrophin preparations, there is an increased risk of having multiple pregnancies. Multiple pregnancies carry an increased health risk for both the mother and her babies around the time of birth. Furthermore, multiple pregnancies and characteristics of the patients undergoing fertility treatment (e.g. age of the female, sperm characteristics) may be associated with an increased risk of congenital abnormalities. There is a slightly increased risk of extra-uterine pregnancy in women with damaged fallopian tubes.

In women undergoing fertility treatment there may be a slightly higher risk of miscarriage.

Breast-feeding

You should not use Fertavid if you are breast-feeding.

Driving and using machines

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

3. HOW TO USE FERTAVID
Always use Fertavid exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Dosage in women**

Your doctor will decide on the dose of Fertavid to be given. This dose may be adjusted as your treatment progresses. Further details on the treatment schedule are given below.

There are large differences between women in the response of the ovaries to FSH, which makes it impossible to set a dosage schedule which is suitable for all patients. To find the right dosage, follicle growth is checked by means of ultrasound scanning, and measurement of the amount of estradiol (female sex hormone) in blood or urine.

- **Women who are not ovulating**
  Initially, a starting dose is set by your doctor. This dose is continued for at least seven days. If there is no ovarian response, the daily dose will then be gradually increased until follicle growth and/or plasma 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 Fertavid is then stopped and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

- **Medically assisted reproduction programs, e.g. IVF**
  A starting dose is set by your doctor. This dose is continued for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their ovarian response. 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.

**Dosage in men**

Fertavid is usually prescribed at a dose of 450 IU/week, mostly in 3 dosages of 150 IU, in combination with another hormone (hCG), for at least 3 to 4 months. If you have not responded after this period, your treatment may carry on for at least 18 months.

**Method and route of administration**

Fertavid only works if it is injected in a muscle or under the skin.

The very first injection of Fertavid should be given under medical supervision. 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 (intramuscular) should only be given by a doctor or a nurse.

Injections under the skin (subcutaneous) may, in some cases, be given by you or your partner. Your doctor will tell you when and how to do this. When the instructions are followed carefully, Fertavid will be administered properly and with minimal discomfort.

**Instructions for use**

**Step 1 - Preparing the syringe**

Sterile disposable syringes and needles should be used for administration of Fertavid. The volume of the syringe should be small enough so that the prescribed dose can be given with reasonable accuracy. Fertavid solution for injection comes in a glass vial. Do not use if the solution contains particles or is not clear. First, remove the flip-off cap of the vial. Place a needle on a syringe and pierce the needle through the rubber stopper of the vial (a). Draw the solution up into the syringe (b), and replace the needle with an injection needle (c). Finally hold the syringe with the needle pointing upwards and gently tap the side to force any air bubbles up to the top; then squeeze the plunger until all the air has been expelled, and only Fertavid solution is left in the syringe (d). If necessary, the plunger may be squeezed further, to adjust the volume to be administered.
Step 2 - The injection site
The best site for subcutaneous injection is in the abdomen around the navel (e) where there is a lot of loose skin and layers of fatty tissue. You should vary the injection site a little with each injection. It is possible to inject in other areas. Your doctor or nurse will advise you where to inject.

Step 3 - Preparing the area
A few taps at the injection site will stimulate tiny nerve endings and help reduce discomfort when the needle goes in. Hands should be washed and the injection site swabbed with disinfectant (for example chlorohexidine 0.5%) to remove any surface bacteria. Clean about two inches around the point where the needle will go in and let the disinfectant dry for at least one minute before proceeding.

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

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

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

Step 7 - Removing the syringe
Pull the syringe out quickly and apply pressure to the injection site with a swab containing disinfectant. A gentle massage of the site - while still maintaining pressure - helps disperse the Fertavid solution and relieve any discomfort.

Any remaining solution should be discarded.
Do not mix Fertavid with any other medicines.

If you use more Fertavid than you should
Inform your doctor.
Too high a dose may cause overstimulation of the ovaries. See section on Possible side effects below.
If you forget to use Fertavid

Do not take a double dose to make up for a forgotten dose.
Do tell your doctor that you missed a dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fertavid can cause side effects, although not everybody gets them.
Minor side effects include bruising, pain, redness, swelling and itching at the site of the injection.
Occasionally, more widespread reactions like rash have been observed.

If you are a woman:
A complication with FSH treatment is unwanted overstimulation of the ovaries. This condition can become very serious, but 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.
Rarely, blood clots may occur without unwanted overstimulation of the ovaries (see also “Take special care with Fertavid”).

Other side effects observed in clinical studies include headache and nausea.

If you are a man:
Some breast development or acne may occur due to treatment with hCG.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FERTAVID

Keep out of the reach and sight of children.

Do not use Fertavid after the expiry date which is stated on the label after 'EXP:'.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial(s) in the outer carton.

For your convenience, you may store Fertavid at or below 25 °C (at room temperature) for a single period of not more than 3 months.
Make a note of when you start storing the product out of the refrigerator.

The contents of a vial should be used immediately after piercing the rubber stopper.
Do not use Fertavid if you notice that the solution contains particles or is not clear.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Fertavid contains
The active substance is follitropin beta, a hormone known as follicle-stimulating hormone (FSH) in a strength of 200 IU in 0.5 ml aqueous solution per vial.

The other ingredients are sucrose, sodium citrate, L-methionine and polysorbate 20 in water for injections. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

What Fertavid looks like and contents of the pack

Fertavid solution for injection is a clear, colourless solution. It is supplied in a glass vial. It is available in packs of 1, 5 or 10 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
SP Europe, Rue de Stalle 73, B-1180 Bruxelles, Belgium.

Manufacturer
- N.V. Organon, Kloosterstraat 6, Postbus 20, 5340 BH Oss, The Netherlands
- Organon (Ireland) Ltd., P.O. Box 2857, Drynam Road, Swords, Co. Dublin, Ireland
- SP, Usine Saint Charles, 60590 Eragny sur Epte, France

This leaflet was last approved in

In correspondence please quote the batch number.
Read all of this leaflet carefully before you start using this medicine.

− Keep this leaflet. You may need to read it again.
− If you have any further questions, ask your doctor or pharmacist.
− This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
− If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Fertavid is and what it is used for
2. Before you use Fertavid
3. How to use Fertavid
4. Possible side effects
5. How to store Fertavid
6. Further information

1. WHAT FERTAVID IS AND WHAT IT IS USED FOR

Fertavid 150 IU/0.18 ml solution for injection contains a hormone known as follicle-stimulating hormone (FSH) in a strength of 833 IU/ml.
FSH belongs to the group of gonadotrophins, which 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. In men, FSH is needed for the production of sperm.

Fertavid is used to treat infertility in any of the following situations:
• In women who are not ovulating, Fertavid can be used to cause ovulation in women who have not responded to treatment with clomifene citrate.
• In women undergoing assisted reproduction techniques, including in vitro fertilisation (IVF) and other methods, Fertavid can be used to bring about the development of multiple follicles.
• In men who are infertile due to a hormonal deficiency, Fertavid can be used for the production of sperm.

2. BEFORE YOU USE FERTAVID

Do not use Fertavid

• if you have a tumour of the ovary, breast, uterus, testis, pituitary gland or hypothalamus
• if you are allergic (hypersensitive) to follitropin beta or any of the other ingredients of Fertavid
• if you have heavy or irregular vaginal bleeding where the cause is not known
• if you suffer from primary ovarian failure
• if you have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD)
• if you have malformations of the sexual organs which make a normal pregnancy impossible
• if you have fibroids in the uterus which make a normal pregnancy impossible
• if you suffer from primary testicular failure.

Take special care with Fertavid
Please inform your doctor if you have experienced an allergic reaction to neomycin and/or streptomycin (antibiotics) in the past.

If you are a woman:
Close supervision by your 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 your doctor to choose the correct dose of Fertavid 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 your 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.

Treatment with Fertavid (like pregnancy itself) may increase the risk of thrombosis (the formation of a blood clot in a blood vessel, most often in the veins of the legs or the lungs). Please discuss this with your doctor, before starting treatment, especially if:
• you already know you have an increased risk of thrombosis
• you, or anyone in your immediate family, have ever had a thrombosis
• you are severely overweight.

If you are a man:
Elevated FSH blood levels are indicative of testicular damage. Fertavid is usually not effective in such cases. To monitor treatment, your doctor may ask you for a semen analysis to be performed 4 to 6 months after the beginning of treatment.

Using other medicines
If Fertavid is used in combination with clomifene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Fertavid may be needed to achieve a response. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy
There is neither clinical experience nor evidence from studies in animals that use of Fertavid during pregnancy might lead to congenital abnormalities. Nevertheless, you should not use Fertavid if you are already pregnant, or suspect that you might be pregnant.

After treatment with gonadotrophin preparations, there is an increased risk of having multiple pregnancies. Multiple pregnancies carry an increased health risk for both the mother and her babies around the time of birth. Furthermore, multiple pregnancies and characteristics of the patients undergoing fertility treatment (e.g. age of the female, sperm characteristics) may be associated with an increased risk of congenital abnormalities. There is a slightly increased risk of extra-uterine pregnancy in women with damaged fallopian tubes. In women undergoing fertility treatment there may be a slightly higher risk of miscarriage.

Breast-feeding
You should not use Fertavid if you are breast-feeding.

Driving and using machines
No effects on the ability to drive and use machines have been observed.

3. HOW TO USE FERTAVID
Always use Fertavid exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Dosage in women**

Your doctor will decide on the dose of Fertavid to be given. This dose may be adjusted as your treatment progresses. Further details on the treatment schedule are given below.

There are large differences between women in the response of the ovaries to FSH, which makes it impossible to set a dosage schedule which is suitable for all patients. To find the right dosage, follicle growth is checked by means of ultrasound scanning, and measurement of the amount of estradiol (female sex hormone) in blood or urine.

- **Women who are not ovulating**
  Initially, a starting dose is set by your doctor. This dose is continued for at least seven days. If there is no ovarian response, the daily dose will then be gradually increased until follicle growth and/or plasma 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 Fertavid is then stopped and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

- **Medically assisted reproduction programs, e.g. IVF**
  A starting dose is set by your doctor. This dose is continued for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their ovarian response. 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.

**Dosage in men**

Fertavid is usually prescribed at a dose of 450 IU/week, mostly in 3 dosages of 150 IU, in combination with another hormone (hCG), for at least 3 to 4 months. If you have not responded after this period, your treatment may carry on for at least 18 months.

**Method and route of administration**

Fertavid solution for injection in cartridges has been developed for use in a pen injector called Puregon Pen. The separate instructions for using the pen must be followed carefully. Do not use the cartridge if the solution contains particles or if the solution is not clear.

Using the pen, injections just under the skin (in the abdominal wall, for example) can be given by you or your partner. Your doctor will tell you when and how to do this. When the instructions are followed carefully, Fertavid will be administered properly and with minimal discomfort. The very first injection of Fertavid should be given under medical supervision.

**If you use more Fertavid than you should**

Inform your doctor.
Too high a dose may cause overstimulation of the ovaries. See section on Possible side effects below.

**If you forget to use Fertavid**

Do not take a double dose to make up for a forgotten dose.
Do tell your doctor that you missed a dose.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Fertavid can cause side effects, although not everybody gets them.
Minor side effects include bruising, pain, redness, swelling and itching at the site of the injection. Occasionally, more widespread reactions like rash have been observed.

*If you are a woman:*
A complication with FSH treatment is unwanted overstimulation of the ovaries. This condition can become very serious, but 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. Rarely, blood clots may occur without unwanted overstimulation of the ovaries (see also “Take special care with Fertavid”).

Other side effects observed in clinical studies include headache and nausea.

*If you are a man:*
Some breast development or acne may occur due to treatment with hCG.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE FERTAVID**

Keep out of the reach and sight of children.

Do not use Fertavid after the expiry date which is stated on the label after 'EXP:'.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the cartridge in the outer carton.

For your convenience, you may store Fertavid at or below 25 °C (at room temperature) for a single period of not more than 3 months.
Make a note of when you start storing the product out of the refrigerator.

Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days.
Please put the day of first use of the cartridge on the dosing record table as shown in the Instruction Manual of the Puregon Pen.
Do not use Fertavid if you notice that the solution contains particles or is not clear.

Discard used needles immediately after injection.
Fertavid cartridges are not designed to allow any other drug to be mixed in the cartridges.
Empty cartridges must not be refilled.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

What Fertavid contains
• The active substance is follitropin beta, a hormone known as follicle-stimulating hormone (FSH) in a strength of 833 IU/ml aqueous solution per cartridge.
• The other ingredients are sucrose, sodium citrate, L-methionine, polysorbate 20 and benzyl alcohol in water for injections. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

What Fertavid looks like and contents of the pack

Fertavid solution for injection is a clear, colourless solution. It is supplied in a glass cartridge. It is available in packs of 1 cartridge.

Marketing Authorisation Holder

SP Europe, Rue de Stalle 73, B-1180 Bruxelles, Belgium.

Manufacturer

• N.V. Organon, Kloosterstraat 6, Postbus 20, 5340 BH Oss, The Netherlands
• Organon (Ireland) Ltd., P.O. Box 2857, Drynam Road, Swords, Co. Dublin, Ireland

This leaflet was last approved in

In correspondence please quote the batch number.
1. WHAT FERTAVID IS AND WHAT IT IS USED FOR

Fertavid 300 IU/0.36 ml solution for injection contains a hormone known as follicle-stimulating hormone (FSH) in a strength of 833 IU/ml. FSH belongs to the group of gonadotrophins, which 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. In men, FSH is needed for the production of sperm.

Fertavid is used to treat infertility in any of the following situations:

- In women who are not ovulating, Fertavid can be used to cause ovulation in women who have not responded to treatment with clomifene citrate.
- In women undergoing assisted reproduction techniques, including in vitro fertilisation (IVF) and other methods, Fertavid can be used to bring about the development of multiple follicles.
- In men who are infertile due to a hormonal deficiency, Fertavid can be used for the production of sperm.

2. BEFORE YOU USE FERTAVID

Do not use Fertavid

- if you have a tumour of the ovary, breast, uterus, testis, pituitary gland or hypothalamus
- if you are allergic (hypersensitive) to follitropin beta or any of the other ingredients of Fertavid
- if you have heavy or irregular vaginal bleeding where the cause is not known
- if you suffer from primary ovarian failure
- if you have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD)
- if you have malformations of the sexual organs which make a normal pregnancy impossible
- if you have fibroids in the uterus which make a normal pregnancy impossible
- if you suffer from primary testicular failure.

Take special care with Fertavid
Please inform your doctor if you have experienced an allergic reaction to neomycin and/or streptomycin (antibiotics) in the past.

If you are a woman:
Close supervision by your 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 your doctor to choose the correct dose of Fertavid 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 your 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.

Treatment with Fertavid (like pregnancy itself) may increase the risk of thrombosis (the formation of a blood clot in a blood vessel, most often in the veins of the legs or the lungs). Please discuss this with your doctor, before starting treatment, especially if:
- you already know you have an increased risk of thrombosis
- you, or anyone in your immediate family, have ever had a thrombosis
- you are severely overweight.

If you are a man:
Elevated FSH blood levels are indicative of testicular damage. Fertavid is usually not effective in such cases. To monitor treatment, your doctor may ask you for a semen analysis to be performed 4 to 6 months after the beginning of treatment.

Using other medicines
If Fertavid is used in combination with clomifene citrate there may be an increased follicular response.
If a GnRH agonist has been given, higher doses of Fertavid may be needed to achieve a response.
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy
There is neither clinical experience nor evidence from studies in animals that use of Fertavid during pregnancy might lead to congenital abnormalities. Nevertheless, you should not use Fertavid if you are already pregnant, or suspect that you might be pregnant.
After treatment with gonadotrophin preparations, there is an increased risk of having multiple pregnancies. Multiple pregnancies carry an increased health risk for both the mother and her babies around the time of birth. Furthermore, multiple pregnancies and characteristics of the patients undergoing fertility treatment (e.g. age of the female, sperm characteristics) may be associated with an increased risk of congenital abnormalities. There is a slightly increased risk of extra-uterine pregnancy in women with damaged fallopian tubes.
In women undergoing fertility treatment there may be a slightly higher risk of miscarriage.

Breast-feeding
You should not use Fertavid if you are breast-feeding.

Driving and using machines
No effects on the ability to drive and use machines have been observed.

3. HOW TO USE FERTAVID
Always use Fertavid exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Dosage in women**

Your doctor will decide on the dose of Fertavid to be given. This dose may be adjusted as your treatment progresses. Further details on the treatment schedule are given below. There are large differences between women in the response of the ovaries to FSH, which makes it impossible to set a dosage schedule which is suitable for all patients. To find the right dosage, follicle growth is checked by means of ultrasound scanning, and measurement of the amount of estradiol (female sex hormone) in blood or urine.

- **Women who are not ovulating**
  Initially, a starting dose is set by your doctor. This dose is continued for at least seven days. If there is no ovarian response, the daily dose will then be gradually increased until follicle growth and/or plasma 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 Fertavid is then stopped and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

- **Medically assisted reproduction programs, e.g. IVF**
  A starting dose is set by your doctor. This dose is continued for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their ovarian response. 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.

**Dosage in men**

Fertavid is usually prescribed at a dose of 450 IU/week, mostly in 3 dosages of 150 IU, in combination with another hormone (hCG), for at least 3 to 4 months. If you have not responded after this period, your treatment may carry on for at least 18 months.

**Method and route of administration**

Fertavid solution for injection in cartridges has been developed for use in a pen injector called Puregon Pen. The separate instructions for using the pen must be followed carefully. Do not use the cartridge if the solution contains particles or if the solution is not clear. Using the pen, injections just under the skin (in the abdominal wall, for example) can be given by you or your partner. Your doctor will tell you when and how to do this. When the instructions are followed carefully, Fertavid will be administered properly and with minimal discomfort. The very first injection of Fertavid should be given under medical supervision.

**If you use more Fertavid than you should**

Inform your doctor.
Too high a dose may cause overstimulation of the ovaries. See section on Possible side effects below.

**If you forget to use Fertavid**

Do not take a double dose to make up for a forgotten dose.
Do tell your doctor that you missed a dose.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Fertavid can cause side effects, although not everybody gets them.
Minor side effects include bruising, pain, redness, swelling and itching at the site of the injection. Occasionally, more widespread reactions like rash have been observed.

If you are a woman:
A complication with FSH treatment is unwanted overstimulation of the ovaries. This condition can become very serious, but 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. Rarely, blood clots may occur without unwanted overstimulation of the ovaries (see also “Take special care with Fertavid”).

Other side effects observed in clinical studies include headache and nausea.

If you are a man:
Some breast development or acne may occur due to treatment with hCG.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FERTAVID

Keep out of the reach and sight of children.

Do not use Fertavid after the expiry date which is stated on the label after 'EXP:'.

Store in a refrigerator (2 °C – 8 ºC).
Do not freeze.
Keep the cartridge in the outer carton.

For your convenience, you may store Fertavid at or below 25 ºC (at room temperature) for a single period of not more than 3 months. Make a note of when you start storing the product out of the refrigerator.

Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days.
Please put the day of first use of the cartridge on the dosing record table as shown in the Instruction Manual of the Puregon Pen.
Do not use Fertavid if you notice that the solution contains particles or is not clear.

Discard used needles immediately after injection.
Fertavid cartridges are not designed to allow any other drug to be mixed in the cartridges. Empty cartridges must not be refilled.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Fertavid contains
The active substance is follitropin beta, a hormone known as follicle-stimulating hormone (FSH) in a strength of 833 IU/ml aqueous solution per cartridge.

The other ingredients are sucrose, sodium citrate, L-methionine, polysorbate 20 and benzyl alcohol in water for injections. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

What Fertavid looks like and contents of the pack

Fertavid solution for injection is a clear, colourless solution. It is supplied in a glass cartridge. It is available in packs of 1 cartridge.

Marketing Authorisation Holder
SP Europe, Rue de Stalle 73, B-1180 Bruxelles, Belgium.

Manufacturer
- N.V. Organon, Kloosterstraat 6, Postbus 20, 5340 BH Oss, The Netherlands
- Organon (Ireland) Ltd., P.O. Box 2857, Drynam Road, Swords, Co. Dublin, Ireland

This leaflet was last approved in

In correspondence please quote the batch number.
Fertavid 600 IU/0.72 ml solution for injection
follitropin beta

Read all of this leaflet carefully before you start using this medicine.
− Keep this leaflet. You may need to read it again.
− If you have any further questions, ask your doctor or pharmacist.
− This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
− If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Fertavid is and what it is used for
2. Before you use Fertavid
3. How to use Fertavid
4. Possible side effects
5. How to store Fertavid
6. Further information

1. WHAT FERTAVID IS AND WHAT IT IS USED FOR

Fertavid 600 IU/0.72 ml solution for injection contains a hormone known as follicle-stimulating hormone (FSH) in a strength of 833 IU/ml.
FSH belongs to the group of gonadotrophins, which 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. In men, FSH is needed for the production of sperm.

Fertavid is used to treat infertility in any of the following situations:
• In women who are not ovulating, Fertavid can be used to cause ovulation in women who have not responded to treatment with clomifene citrate.
• In women undergoing assisted reproduction techniques, including in vitro fertilisation (IVF) and other methods, Fertavid can be used to bring about the development of multiple follicles.
• In men who are infertile due to a hormonal deficiency, Fertavid can be used for the production of sperm.

2. BEFORE YOU USE FERTAVID

Do not use Fertavid
• if you have a tumour of the ovary, breast, uterus, testis, pituitary gland or hypothalamus
• if you are allergic (hypersensitive) to follitropin beta or any of the other ingredients of Fertavid
• if you have heavy or irregular vaginal bleeding where the cause is not known
• if you suffer from primary ovarian failure
• if you have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD)
• if you have malformations of the sexual organs which make a normal pregnancy impossible
• if you have fibroids in the uterus which make a normal pregnancy impossible
• if you suffer from primary testicular failure.

Take special care with Fertavid
Please inform your doctor if you have experienced an allergic reaction to neomycin and/or streptomycin (antibiotics) in the past.

If you are a woman:
Close supervision by your 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 your doctor to choose the correct dose of Fertavid 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 your 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.

Treatment with Fertavid (like pregnancy itself) may increase the risk of thrombosis (the formation of a blood clot in a blood vessel, most often in the veins of the legs or the lungs). Please discuss this with your doctor, before starting treatment, especially if:
- you already know you have an increased risk of thrombosis
- you, or anyone in your immediate family, have ever had a thrombosis
- you are severely overweight.

If you are a man:
Elevated FSH blood levels are indicative of testicular damage. Fertavid is usually not effective in such cases. To monitor treatment, your doctor may ask you for a semen analysis to be performed 4 to 6 months after the beginning of treatment.

Using other medicines

If Fertavid is used in combination with clomifene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Fertavid may be needed to achieve a response. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy

There is neither clinical experience nor evidence from studies in animals that use of Fertavid during pregnancy might lead to congenital abnormalities. Nevertheless, you should not use Fertavid if you are already pregnant, or suspect that you might be pregnant.

After treatment with gonadotrophin preparations, there is an increased risk of having multiple pregnancies. Multiple pregnancies carry an increased health risk for both the mother and her babies around the time of birth. Furthermore, multiple pregnancies and characteristics of the patients undergoing fertility treatment (e.g. age of the female, sperm characteristics) may be associated with an increased risk of congenital abnormalities. There is a slightly increased risk of extra-uterine pregnancy in women with damaged fallopian tubes.

In women undergoing fertility treatment there may be a slightly higher risk of miscarriage.

Breast-feeding

You should not use Fertavid if you are breast-feeding.

Driving and using machines

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

3. **HOW TO USE FERTAVID**
Always use Fertavid exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Dosage in women

Your doctor will decide on the dose of Fertavid to be given. This dose may be adjusted as your treatment progresses. Further details on the treatment schedule are given below. There are large differences between women in the response of the ovaries to FSH, which makes it impossible to set a dosage schedule which is suitable for all patients. To find the right dosage, follicle growth is checked by means of ultrasound scanning, and measurement of the amount of estradiol (female sex hormone) in blood or urine.

- Women who are not ovulating
  Initially, a starting dose is set by your doctor. This dose is continued for at least seven days. If there is no ovarian response, the daily dose will then be gradually increased until follicle growth and/or plasma 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 Fertavid is then stopped and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

- Medically assisted reproduction programs, e.g. IVF
  A starting dose is set by your doctor. This dose is continued for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their ovarian response. 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.

Dosage in men

Fertavid is usually prescribed at a dose of 450 IU/week, mostly in 3 dosages of 150 IU, in combination with another hormone (hCG), for at least 3 to 4 months. If you have not responded after this period, your treatment may carry on for at least 18 months.

Method and route of administration

Fertavid solution for injection in cartridges has been developed for use in a pen injector called Puregon Pen. The separate instructions for using the pen must be followed carefully. Do not use the cartridge if the solution contains particles or if the solution is not clear.

Using the pen, injections just under the skin (in the abdominal wall, for example) can be given by you or your partner. Your doctor will tell you when and how to do this. When the instructions are followed carefully, Fertavid will be administered properly and with minimal discomfort.

The very first injection of Fertavid should be given under medical supervision.

If you use more Fertavid than you should

Inform your doctor.
Too high a dose may cause overstimulation of the ovaries. See section on Possible side effects below.

If you forget to use Fertavid

Do not take a double dose to make up for a forgotten dose.
Do tell your doctor that you missed a dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fertavid can cause side effects, although not everybody gets them.
Minor side effects include bruising, pain, redness, swelling and itching at the site of the injection. Occasionally, more widespread reactions like rash have been observed.

If you are a woman:
A complication with FSH treatment is unwanted overstimulation of the ovaries. This condition can become very serious, but 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.

Rarely, blood clots may occur without unwanted overstimulation of the ovaries (see also “Take special care with Fertavid”).

Other side effects observed in clinical studies include headache and nausea.

If you are a man:
Some breast development or acne may occur due to treatment with hCG.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FERTAVID

Keep out of the reach and sight of children.

Do not use Fertavid after the expiry date which is stated on the label after 'EXP:'.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the cartridge in the outer carton.

For your convenience, you may store Fertavid at or below 25 °C (at room temperature) for a single period of not more than 3 months.
Make a note of when you start storing the product out of the refrigerator.

Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days.
Please put the day of first use of the cartridge on the dosing record table as shown in the Instruction Manual of the Puregon Pen.
Do not use Fertavid if you notice that the solution contains particles or is not clear.

Discard used needles immediately after injection.
Fertavid cartridges are not designed to allow any other drug to be mixed in the cartridges.
Empty cartridges must not be refilled.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Fertavid contains
• The active substance is follitropin beta, a hormone known as follicle-stimulating hormone (FSH) in a strength of 833 IU/ml aqueous solution per cartridge.
• The other ingredients are sucrose, sodium citrate, L-methionine, polysorbate 20, benzyl alcohol in water for injections. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

What Fertavid looks like and contents of the pack

Fertavid solution for injection is a clear, colourless solution. It is supplied in a glass cartridge. It is available in packs of 1 cartridge.

Marketing Authorisation Holder
SP Europe, Rue de Stalle 73, B-1180 Bruxelles, Belgium.

Manufacturer
• N.V. Organon, Kloosterstraat 6, Postbus 20, 5340 BH Oss, The Netherlands
• Organon (Ireland) Ltd., P.O. Box 2857, Drynam Road, Swords, Co. Dublin, Ireland

This leaflet was last approved in

In correspondence please quote the batch number.
Read all of this leaflet carefully before you start using this medicine.

− Keep this leaflet. You may need to read it again.
− If you have any further questions, ask your doctor or pharmacist.
− This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
− If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Fertavid is and what it is used for
2. Before you use Fertavid
3. How to use Fertavid
4. Possible side effects
5. How to store Fertavid
6. Further information

1. WHAT FERTAVID IS AND WHAT IT IS USED FOR

Fertavid 900 IU/1.08 ml solution for injection contains a hormone known as follicle-stimulating hormone (FSH) in a strength of 833 IU/ml.
FSH belongs to the group of gonadotrophins, which 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. In men, FSH is needed for the production of sperm.

Fertavid is used to treat infertility in any of the following situations:
• In women who are not ovulating, Fertavid can be used to cause ovulation in women who have not responded to treatment with clomifene citrate.
• In women undergoing assisted reproduction techniques, including in vitro fertilisation (IVF) and other methods, Fertavid can be used to bring about the development of multiple follicles.
• In men who are infertile due to a hormonal deficiency, Fertavid can be used for the production of sperm.

2. BEFORE YOU USE FERTAVID

Do not use Fertavid
• if you have a tumour of the ovary, breast, uterus, testis, pituitary gland or hypothalamus
• if you are allergic (hypersensitive) to follitropin beta or any of the other ingredients of Fertavid
• if you have heavy or irregular vaginal bleeding where the cause is not known
• if you suffer from primary ovarian failure
• if you have ovarian cysts or enlarged ovaries not caused by polycystic ovarian disease (PCOD)
• if you have malformations of the sexual organs which make a normal pregnancy impossible
• if you have fibroids in the uterus which make a normal pregnancy impossible
• if you suffer from primary testicular failure.

Take special care with Fertavid:
Please inform your doctor if you have experienced an allergic reaction to neomycin and/or streptomycin (antibiotics) in the past.

If you are a woman:
Close supervision by your 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 your doctor to choose the correct dose of Fertavid 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 your 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.

Treatment with Fertavid (like pregnancy itself) may increase the risk of thrombosis (the formation of a blood clot in a blood vessel, most often in the veins of the legs or the lungs). Please discuss this with your doctor, before starting treatment, especially if:
- you already know you have an increased risk of thrombosis
- you, or anyone in your immediate family, have ever had a thrombosis
- you are severely overweight.

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Elevated FSH blood levels are indicative of testicular damage. Fertavid is usually not effective in such cases. To monitor treatment, your doctor may ask you for a semen analysis to be performed 4 to 6 months after the beginning of treatment.

Using other medicines
If Fertavid is used in combination with clomifene citrate there may be an increased follicular response. If a GnRH agonist has been given, higher doses of Fertavid may be needed to achieve a response. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy
There is neither clinical experience nor evidence from studies in animals that use of Fertavid during pregnancy might lead to congenital abnormalities. Nevertheless, you should not use Fertavid if you are already pregnant, or suspect that you might be pregnant.

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In women undergoing fertility treatment there may be a slightly higher risk of miscarriage.

Breast-feeding
You should not use Fertavid if you are breast-feeding.

Driving and using machines
No effects on the ability to drive and use machines have been observed.

3. HOW TO USE FERTAVID
Always use Fertavid exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Dosage in women**

Your doctor will decide on the dose of Fertavid to be given. This dose may be adjusted as your treatment progresses. Further details on the treatment schedule are given below.

There are large differences between women in the response of the ovaries to FSH, which makes it impossible to set a dosage schedule which is suitable for all patients. To find the right dosage, follicle growth is checked by means of ultrasound scanning, and measurement of the amount of estradiol (female sex hormone) in blood or urine.

- **Women who are not ovulating**
  
  Initially, a starting dose is set by your doctor. This dose is continued for at least seven days. If there is no ovarian response, the daily dose will then be gradually increased until follicle growth and/or plasma 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 Fertavid is then stopped and ovulation can be induced by administering human chorionic gonadotrophin (hCG).

- **Medically assisted reproduction programs, e.g. IVF**
  
  A starting dose is set by your doctor. This dose is continued for at least the first four days. After this, the dose may be adjusted for the individual patient, based upon their ovarian response. 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.

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**If you use more Fertavid than you should**

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**If you forget to use Fertavid**

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Rarely, blood clots may occur without unwanted overstimulation of the ovaries (see also “Take special care with Fertavid”).

Other side effects observed in clinical studies include headache and nausea.

*If you are a man:*
Some breast development or acne may occur due to treatment with hCG.

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5. **HOW TO STORE FERTAVID**

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Store in a refrigerator (2 °C – 8 °C).
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