NEW ZEALAND DATA SHEET

1 PRODUCT NAME

PUREGON 150 IU, 300 IU, 600 IU, 900 IU Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

150 IU cartridge: a clear, colourless, aqueous solution containing 833 IU FSH (follitropin beta) per mL.

Total volume = 0.270 mL

300 IU cartridge: a clear, colourless, aqueous solution containing 833 IU FSH (follitropin beta) per mL.

Total volume 0.480 mL (= 437 IU)

600 IU cartridge: a clear, colourless aqueous solution containing 833 IU FSH (follitropin beta) per mL.

Total volume 0.840 mL (= 737 IU)

900 IU cartridge: a clear, colourless, aqueous solution containing 833 IU FSH (follitropin beta) per mL.

Total volume = 1.230 mL

Cartridges contain 833 IU of FSH activity per mL aqueous solution. Cartridges with a net dose of 150 IU contain a minimum of 225 IU in 0.270 mL; those of 300 IU contain a minimum of 400 IU in 0.480 mL; those of 600 IU contain a minimum of 700 IU in 0.840 mL; those of 900 IU contain a minimum of 1,025 IU in 1.230 mL.

PUREGON cartridges contain the active substance follitropin beta (recombinant follicle-stimulating hormone, FSH 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 mcg of protein/mL (specific *in vivo* bioactivity equal to approximately 10,000 IU FSH/mg protein). One cartridge contains a net total dose of 150 IU, 300 IU, 600 IU or 900 IU. Total dosings are limited to 3 (150 IU cartridge), 6 (300 or 600 IU cartridges), or 9 (900 IU cartridge).

Excipients with known effect:

- benzyl alcohol

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

In cartridges, designed to be used in conjunction with a pen injector.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the female

- Anovulatory infertility
- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programmes [e.g. *in vitro* fertilisation and related procedures].

In the male

- Deficient spermatogenesis due to hypogonadotrophic hypogonadism.

4.2 Dose and method of administration

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

Dose

Dosage in the female

Anovulation/defective follicle ripening and/or corpus luteum insufficiency

There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotropins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasound assessment of follicular development. The concurrent determination of serum estradiol levels may also be useful.

A sequential treatment scheme is recommended starting with daily administration of 50 IU PUREGON. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma estradiol levels indicate an adequate pharmacodynamic response.

A daily ascent rate of 40-100% is considered to be optimal. The daily effective dose is then maintained until pre-ovulatory conditions are reached. If oestrogen levels rise too rapidly, i.e. more than a daily doubling for 2 or 3 consecutive days, the daily dose should be decreased.

Pre-ovulatory conditions are reached when plasma oestradiol levels of 300-900 picogram/mL (1000-3000 pmol/L), or a total urinary oestrogen excretion of 75-200 microgram (250-650 nmol)/24 hours are attained, and/or when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter. The administration of PUREGON is then discontinued and ovulation can be induced by administering human chorionic gonadotropin (hCG) in a dose of 5000-10,000 IU. Two to three injections of 1000-3000 IU hCG each may be given within the following 9 days to prevent insufficiency of the corpus luteum.

Since follicles of over 15 mm may produce pregnancies, a maximum of two additional follicles exceeding 15 mm is acceptable. If this limit is exceeded, hCG should be withheld and pregnancy should be avoided in order to prevent large multiple gestations.

In women with polycystic ovarian disease, induction of a hypogonadotropic state by a GnRH agonist before and during treatment with PUREGON may result in better pregnancy rates than without the use of an agonist.

Controlled ovarian hyperstimulation in medically assisted reproduction programmes

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 on ovarian response. Stimulation of follicular growth is generally achieved by daily administration of 75-300 IU FSH. PUREGON can be given either alone, or in combination with clomiphene citrate to stimulate the endogenous production of gonadotropins, or in combination with a GnRH agonist, in particular to prevent premature luteinization.

Maturation of follicles is monitored by ultrasound assessment. The concurrent determination of serum estradiol levels may also be useful. When ultrasound assessment indicates the presence of at least three follicles of 16-20 mm, and there is evidence of a good estradiol response (plasma levels of about 300-400 picogram/mL (1000-1300 pmol/L) for each follicle with a diameter greater than 18 mm), the final phase of maturation of the follicles is induced 30-40 hours after the last administration of PUREGON by administration of hCG in a dose of 5000-10,000 IU oocyte retrieval is performed 34-35 hours later.

Dosage in the male
75 IU FSH injections are given daily or 2-3 times a week. These injections should be combined with a simultaneous dose of 1000-2000 IU hCG, 2-3 times a week to make up the necessary LH activity. This treatment should be continued for at least three months before any improvement in spermatogenesis can be expected. During this treatment testosterone replacement therapy should be suspended. Once achieved, the improvement may in some cases be maintained by hCG alone.

Paediatric Population

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

Method of administration

PUREGON Solution for Injection in cartridges has been developed for use in the PUREGON Pen and should be administered **subcutaneously**. The injection site should be alternated to prevent lipoatrophy.

Using the pen, injection of PUREGON can be carried out by the patient herself or partner, provided that proper instructions are given by the physician. Self administration of PUREGON should only be performed by women who are well-motivated, adequately trained and with access to expert advice.

Do not use if the solution contains particles or if the solution is not clear. Each cartridge is for individual patient use only.

Empty cartridges must not be refilled. PUREGON cartridges are not designed to allow any other drug to be mixed in the cartridges.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in **Section 6.1 List of excipients.**
- Tumours of ovarium, breasts, uterus, testes, hypothalamus and pituitary gland.
- Pregnancy
- Unexplained vaginal bleeding
- Ovarian enlargement or cyst not due to polycystic ovarian disease, ovarian, uterine or mammary carcinoma.
- PUREGON is contraindicated when an effective response cannot be obtained, such as:
  - primary ovarian failure such as indicated by high levels of FSH
  - organic disorders of the reproductive organs incompatible with pregnancy such as congenital malformations of the uterus and fibroids
- Any condition in which a pregnancy (including multiple pregnancy) would be particularly hazardous (e.g. extremes of weight disorders and uterine abnormalities).
- Primary testicular failure.
- PUREGON should not be used in the elderly or in children.

4.4 Special warnings and precautions for use

- Before starting treatment, the couple's infertility should be assessed as appropriate. In particular, patients should be evaluated for hypothyroidism, adrenocortical insufficiency, hyperprolactinemia and pituitary or hypothalamic tumours, and appropriate specific treatment given.
- Prior to treating patients for inadequate gonadal function, the following should be assessed:
  (i) Careful clinical examination to determine general, pelvic or genital pathology
  (ii) Serum gonadotrophin levels concentrations to exclude gonadal failure
  (iii) Thyroid function, serum prolactin to exclude endocrinopathies that may be responsible
  (iv) A semen analysis of the partner
- Ovarian torsion has been reported after treatment with gonadotrophins, including PUREGON. Ovarian torsion may be associated with other risk factors such as Ovarian Hyperstimulation Syndrome (OHSS), pregnancy, previous abdominal surgery, past history of ovarian torsion, previous or current cyst and polycystic ovaries. Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion.
- Multiple pregnancies and births have been reported for all gonadotropin treatments, including PUREGON. Multiple gestations, especially high order, carry an increased risk of adverse maternal (pregnancy and delivery complications) and perinatal (low birth weight) outcomes. For anovulatory women undergoing ovulation induction, monitoring follicular development with transvaginal ultrasonography is important for minimising the risk of multi-foetal gestations. The concurrent determination of serum estradiol levels may also be useful. The parents should be advised of the potential risks of multiple births before starting treatment.
- In women undergoing ART procedures, the risk of a multiple pregnancy is mainly related to the number of embryos transferred. When used for an ovulation induction cycle, appropriate FSH dose adjustment(s) should prevent multiple follicle development.
- The first injection of PUREGON should be performed under direct medical supervision.
- Infertile women undergoing ART have an increased incidence of ectopic pregnancies. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.
- Rates of pregnancy loss in women undergoing ART are higher than in the normal population.
- The incidence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This slightly higher incidence is thought to be related to differences in parental characteristics (e.g. maternal age, sperm characteristics) and to the higher incidence of multiple gestations after ART. Analysis of pooled data does not indicate that the use of gonadotrophins in ovulation induction and medically assisted reproduction programmes carries an increased risk of congenital malformations.
- 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 established whether or not treatment with gonadotrophins increases the risk of these tumours in infertile women.
- PUREGON would not be expected to be effective in the absence of endogenous luteinising hormone (LH). The presence of spontaneous or progestogen withdrawal menstruation is suggestive of adequate endogenous LH.
- Thromboembolic events, both in association with and separate from OHSS, have been reported following treatment with gonadotropins, including PUREGON. Intravascular thrombosis, which may originate in venous or arterial vessels, can result in reduced blood flow to vital organs or the extremities. In women with generally recognised risk factors for thromboembolic events, such as a personal or family history, severe obesity or thrombophilia, treatment with gonadotropins, including PUREGON, may further increase this risk. In these women the benefits of gonadotropin administration, including

PUREGON, need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.

- PUREGON 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 PUREGON/hCG therapy.
- In men, semen analysis is recommended 4 to 6 months after the beginning of treatment in assessing the response.
- Medical conditions that contraindicate pregnancy should be evaluated before starting treatment with PUREGON.

Overstimulation of the Ovary During PUREGON Therapy

Ovarian enlargement

Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain occurs in approximately 20% of those treated with PUREGON and hCG and generally regresses without treatment within two or three weeks.

In order to minimise the hazard associated with the occasional abnormal ovarian enlargement which may occur with PUREGON-hCG therapy, the lowest dose consistent with expectation of good results should be used. Careful monitoring of ovarian response can further minimise the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of PUREGON therapy, hCG should not be administered in this course of therapy; this will reduce the chances of development of the Ovarian Hyperstimulation Syndrome.

The Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS may progress rapidly to become a serious medical event. It is characterised by an apparent dramatic increase in vascular permeability which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax and potentially, the pericardium. Clinical signs and symptoms of mild and moderate OHSS are abdominal pain, nausea, diarrhoea, mild to moderate enlargement of ovaries and ovarian cysts. Severe OHSS may be life-threatening. Clinical signs and symptoms of severe OHSS are large ovarian cysts, acute abdominal pain, ascites, pleural effusion, hydrothorax, dyspnea, oliguria, haematological abnormalities and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS. Transient liver function test abnormalities suggestive of hepatic dysfunction with or without morphologic changes on liver biopsy have also been reported in association with OHSS. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting and weight gain. The following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhoea, severe ovarian enlargement, weight gain, dyspnoea and oliguria. Clinical evaluation may reveal hypovolaemia haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress and thromboembolic events (see **Pulmonary and Vascular Complications**).

OHSS may be caused by administration of human Chorionic Gonadotropin (hCG) and by pregnancy (endogenous hCG). Early OHSS usually occurs within 10 days after hCG administration and may be associated with an excessive ovarian response to gonadotropin stimulation. Late OHSS occurs more than 10 days after hCG administration, as a consequence of the hormonal changes with pregnancy. Because of the risk of developing OHSS, patients should be monitored for at least two weeks after hCG administration. OHSS occurs uncommonly in patients when the recommended dose is administered and is more common in patients when higher than recommended doses are administered. Cases of OHSS are more common, more severe and more protracted if pregnancy occurs. Most often, OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten

days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If there is evidence that OHSS may be developing prior to hCG administration, the hCG should be withheld.

Women with known risk factors for a high ovarian response may be especially prone to the development of OHSS during or following treatment with PUREGON. For women having their first cycle of ovarian stimulation, for whom risk factors are only partially known, close observation for early signs and symptoms of OHSS is recommended.

Follow current clinical practice for reducing the risk of OHSS during Assisted Reproductive Technology (ART). Adherence to the recommended Puregon dose and treatment regimen and careful monitoring of ovarian response is important to reduce the risk of OHSS. To monitor the risk of OHSS, ultrasound assessments of follicular development should be performed prior to treatment and at regular intervals during treatment; the concurrent determination of serum estradiol levels may also be useful. In ART there is an increased risk of OHSS with 18 or more follicles of 11 mm or more in diameter.

If OHSS develops, standard and appropriate management of OHSS should be implemented and followed.

If OHSS occurs, treatment should be stopped and the patient hospitalised. Treatment is primarily symptomatic, consisting of bed rest, fluid and electrolyte management and analgesics if needed. The phenomenon of haemoconcentration associated with fluid loss into the peritoneal cavity, pleural cavity and the pericardial cavity has been seen to occur and should be thoroughly assessed in the following manner: (1) fluid intake and output, (2) weight, (3) haematocrit, (4) serum and urinary electrolytes, (5) urine specific gravity, (6) BUN and creatinine, and (7) abdominal girth. These determinations are to be performed daily or more often if the need arises.

With OHSS there is an increased risk of injury to the ovary. The ascetic, pleural and pericardial fluid should not be removed unless absolutely necessary to relieve symptoms such as pulmonary distress or cardiac tamponade. Pelvic examination may cause rupture of an ovarian cyst, which may result in haemoperitoneum, and should therefore be avoided. If this does occur, and if bleeding becomes such that surgery is required, the surgical treatment should be designed to control bleeding and to retain as much ovarian tissue as possible. Intercourse should be prohibited in those patients in whom significant ovarian enlargement occurs after ovulation because of the danger of haemoperitoneum resulting from ruptured ovarian cysts.

The management of OHSS may be divided into three phases: an acute, a chronic, and a resolution phase. Because the use of diuretics can accentuate the diminished intravascular volume, diuretics should be avoided except in the late phase of resolution as described below.

Acute Phase: Management during the acute phase should be designed to prevent haemoconcentration due to loss of intravascular volume to the third space and to minimise the risk of thromboembolic phenomena and kidney damage. Treatment is designed to normalise electrolytes while maintaining an acceptable but somewhat reduced intravascular volume. Full correction of the intravascular volume deficit may lead to an unacceptable increase in the amount of third space fluid accumulation. Management includes administration of limited intravenous fluids, electrolytes, and human serum albumin. Monitoring for the development of hyperkalaemia is recommended.

Chronic Phase: After stabilising the patient during the acute phase, excessive fluid accumulation in the third space should be limited by instituting severe potassium, sodium and fluid restriction.

Resolution Phase: A fall in haematocrit and an increasing urinary output without an increased intake are observed due to the return of third space fluid to the intravascular compartment. Peripheral and/or pulmonary oedema may result if the kidneys are unable to excrete third

space fluid as rapidly as it is mobilised. Diuretics may be indicated during the resolution phase if necessary to combat pulmonary oedema.

Pulmonary and Vascular Complications

Serious pulmonary conditions (e.g. atelectasis, acute respiratory distress syndrome) have been reported. In addition, thromboembolic events both in association with, and separate from the Ovarian Hyperstimulation Syndrome are possible following PUREGON therapy. Intravascular thrombosis, which may originate in venous or arterial vessels, can result in reduced blood flow to vital organs or the extremities. Sequelae of such event have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (Stroke) and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events could result in death.

Multiple Births

In the majority of patients, the pregnancies following treatment with PUREGON resulted in single births. For patients undergoing IVF treatment the risk of multiple pregnancy following assisted reproductive technologies is related to the number of oocytes/embryos replaced, in other patients the incidence of multiple pregnancies is increased by PUREGON, as with other agents used to stimulate ovulation. However, the majority of multiple conceptions are twins. Pregnancy loss is higher than that in the normal population, but comparable with the rates found in women with other fertility problems.

Paediatric population

See **Section 4.2 Dose and method of administration; Section 4.3 Contraindications.**

4.5 Interactions with other medicines and other forms of interactions

Concomitant use of PUREGON and clomiphene citrate may enhance the follicular response. After pituitary desensitization induced by a GnRH agonist, a higher dose of PUREGON may be necessary to elicit an adequate follicular response.

4.6 Fertility, pregnancy and lactation

Pregnancy

(Category B2)
Follitropin beta is not intended for use during pregnancy (see **Section 4.3 Contraindications**). There are no available data from studies in which PUREGON was administered to pregnant animals. In case of inadvertent exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH.

Breast-feeding

There is no information available from clinical or animal studies on the excretion of follitropin beta in milk. It is unlikely that follitropin beta is excreted in human milk due to its high molecular weight. If follitropin beta would be excreted in human milk, it is likely to be degraded in the gastrointestinal tract of the child. However, there are no data available demonstrating this. Follitropin beta may affect milk production.

Fertility

See **Section 4.1 Therapeutic Indications.**

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Unwanted ovarian hyperstimulation, ovarian hyperstimulation syndrome. Signs and symptoms of ovarian hyperstimulation syndrome were reported in 3% of women treated with PUREGON in clinical trials. Multiple pregnancy (including higher order multiplets than twins).

Table 1: Body System Disorders

Percentages of patients with at least one adverse experience classified by body system and reported as related to study medicine pre-marketing in clinical trials[1]		
Body system (WHO system-organ class)	PUREGON n = 1074	Metrodin (Urinary FSH) n = 498
	%	%
Gastrointestinal system disorders		
Nausea	0.5	0.8
Abdominal Pain	0.1	0
Other	3.0	3.4
Reproductive disorders, female[2]		
Hyperstimulation Syndrome	5.2	4.0
Ectopic Pregnancy	2.2	3.4
Abdominal Pain	3.0	3.2
Vaginal Haemorrhage	1.1	0.3
Foetal disorders		
Miscarriage	3.1	4.2
Body as a whole-general disorders		
Pain	0.5	0.2
Influenza -like symptoms	0.2	0.2
Swollen Abdomen	0.2	0
Other	0.3	0.6
Application site disorders		
Injection Site Pain	1.0	0.6

[1] a subject can have adverse experiences in more than one body system.
[2] for this category the number of female patients is used.

Application Site Disorders

Bruising*, pain, redness, swelling, itching.

* In one study of 195 women undergoing superovulation for IVF, comparing intramuscular and subcutaneous routes of administration no differences between the two routes of administration were significant apart from bruising which was more common in the subcutaneous group.

Generalised hypersensitivity reactions which may include erythema, urticaria, rash and pruritus have been observed uncommonly.

In the Female

The table below lists the adverse reactions with PUREGON reported in clinical trials in females according to system organ class and frequency: common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100).

Table 2

SOC	Frequency	Adverse Reaction
Nervous system disorders	Common	Headache
Gastrointestinal disorders	Common	Abdominal distension Abdominal pain
	Uncommon	Abdominal discomfort

		Constipation Diarrhoea Nausea
Reproductive system and breast disorders	Common	OHSS[1] Pelvic pain
	Uncommon	Breast Complaints[2] Metorrhagia Ovarian cyst Ovarian enlargement Ovarian torsion[3] Uterine enlargement Vaginal haemorrhage
General disorders and administration site conditions	Common	Injection site reaction[4]
	Uncommon	Generalised hypersensitivity reaction[5]

[1]Characteristic symptoms of ovarian hyperstimulation and the ovarian hyperstimulation syndrome are included under **Section 4.4 Special Warnings and Precautions for Use.**
[2]Breast complaints include tenderness, pain and/or engorgement and nipple pain
[3]See also **Section 4.4 Special Warnings and Precautions for Use**
[4]Local reactions at the site of injection include: bruising, pain, redness, swelling and itching
[5]Generalised hypersensitivity reaction include erythema, urticaria, rash and pruritus

In rare instances, thromboembolism has been associated with PUREGON/hCG treatment as with other gonadotrophins.

In the Male

The table below lists the adverse reactions with PUREGON reported in a clinical trial in males (30 patients dosed) according to system organ class and frequency: common (≥ 1/100 to < 1/10).

Table 3

SOC	**Frequency[1]**	**Adverse Reaction**
Nervous system disorders	Common	Headache
Skin and subcutaneous tissue disorders	Common	Acne Rash
Reproductive system and breast disorders	Common	Epididymal cyst Gynecomastia
General disorders and administration site conditions	Common	Injection site induration

[1]Adverse reactions that are reported only once are listed as common because a single report raises the frequency above 1%.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

No data on acute toxicity of PUREGON in humans is available, but the acute toxicity of PUREGON and of urinary gonadotrophin preparations in animal studies has been shown to be very low. Too high a dosage for more than one day may lead to hyperstimulation of the

ovaries (see Unwanted Hyperstimulation under **Section 4.4 Special Warnings and Precautions for Use**).

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: gonadotropins; ATC code: G03G A06.

Mechanism of action

PUREGON contains a recombinant FSH. This is produced by recombinant DNA technology, using a Chinese hamster ovary cell line transfected with the human FSH subunit genes. The primary amino acid sequence is identical to that of natural human FSH. Small differences in the carbohydrate chain structure are known to exist.

FSH is indispensable in normal follicular growth and maturation, and gonadal steroid production. In the female the level of FSH is critical for the onset and duration of follicular development, and consequently for the timing and number of follicles reaching maturity. PUREGON can thus be used to stimulate follicular development and steroid production in selected cases of disturbed gonadal function. Furthermore, PUREGON can be used to promote multiple follicular development in medically assisted reproduction programmes [e.g. *in vitro* fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)]. Treatment with PUREGON is generally followed by administration of hCG to induce the final phase of follicle maturation, resumption of meiosis and rupture of the follicle.

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

5.2 Pharmacokinetic properties

Absorption

After subcutaneous administration of PUREGON, high concentrations of FSH are reached within about 12 hours. Due to the sustained release from the injection site and the elimination half-life of about 40 hours (ranging from 12 to 70 hours), FSH levels remain high for 24-48 hours.

Distribution, Biotransformation, Elimination

Due to the relatively long elimination half-life, after repeated administration, plasma concentrations of FSH are approximately 1.5-2.5 times higher than after single administration. This increase contributes to reach therapeutic FSH concentrations.

Since follitropin beta (recombinant FSH) is very similar to endogenous FSH, it is expected that it would be distributed, metabolised, and excreted in the same way.

Bioequivalence Study

A bioequivalence study was performed to compare the pharmacokinetics of FSH after subcutaneous single-dose injection of PUREGON with a conventional syringe as dissolved freeze-dried cake (2 × 75 IU) versus administration of PUREGON Solution (150 IU) with pen-injector.

Due to the precision of the device, it can be assumed that exactly 150 IU was injected with the Pen-injector. The dose injected with the syringe was actually lower than the anticipated

150 IU, which is due to losses while filling the syringe and/or removing excess air and to the void volume of the syringe. After correction of the dose by a factor of 1.18, bioequivalence was demonstrated for all relevant pharmacokinetic parameters (see Table below). Since the daily dose of PUREGON is determined by the patient's individual ovarian response, the slightly higher dose delivered by the Pen is unlikely to affect clinical outcome. The following table shows the main pharmacokinetic results of the study:

Table 4

Parameter	Pen injector (n=20)	Syringe (n=20)	Point estimate	90% CI	Outcome
$AUC_{0-\infty}$ (IU/L.h)	215.1	220.3	1.01	0.93-1.10	bioequivalent
Cmax (IU/L)	3.36	3.43	1.00	0.91-1.11	bioequivalent
Cl app (L/h/kg)	0.0117	0.0122	0.99	0.91-1.08	bioequivalent

5.3 Preclinical safety data

Single-dose administration of PUREGON to rats induced no toxicologically significant effects. In repeated-dose studies in rats (two weeks) and dogs (13 weeks) up to 100-fold the maximal human dose, PUREGON induced no toxicologically significant effects. PUREGON showed no mutagenic potential in the Ames test or in the *in vitro* chromosome aberration test with human lymphocytes.

Carcinogenicity and Mutagenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of follitropin beta. Follitropin beta showed no genotoxic activity in a series of assays performed to evaluate its potential to cause gene mutations (*Salmonella typhimurium* and *E.coli*) and chromosomal damage (human lymphocytes *in vitro*).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sucrose

sodium citrate dihydrate

methionine

polysorbate 20

benzyl alcohol in water for injection

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

The shelf-life of PUREGON solution for injection is three years under the conditions specified under **Section 6.4 Special Precautions for Storage**. PUREGON may be used until the expiration date indicated on the package.

6.4 Special precautions for storage

Keep the cartridge in the outer carton. Keep PUREGON out of reach of children.

Storage by the Pharmacist
Store at 2-8°C. Do not freeze. Protect from light.

Storage by the Patient
There are 2 options:

Either, Store at 2-8°C. Do not freeze.

Or Store below 25°C for a maximum of 3 months.

Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days below 25°C. Protect from light.

6.5 Nature and contents of container

Boxes of PUREGON Solution for Injection contain 1 cartridge of follitropin beta and either 3 (150 IUcartridge), 6 (300 IU and 600 IU cartridges) or 9 (900 IU cartridges) needles to be used with the PUREGON Pen. The cartridges are of colourless hydrolytic (class 1) glass, with a rubber piston and an aluminium crimp-cap with a rubber inlay.

6.6 Special precautions for disposal

Do not use if the solution contains particles or if the solution is not clear.

PUREGON 150 IU, 300 IU, 600 IU or 900 IU Solution for Injection is designed to be used in conjunction with the PUREGON Pen. The instructions for using the pen must be followed carefully. Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

PUREGON cartridges are not designed to allow any other medicine to be mixed in the cartridges. Discard used needles immediately after injection.

Discard used cartridges (including the remaining volume) after the last injection of the treatment cycle.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Organon New Zealand Limited
Level 7, 36 Brandon Street

Wellington 6011
Tel: 0800 111 700

9 DATE OF FIRST APPROVAL

16 March 2000

10 DATE OF REVISION OF THE TEXT

20 January 2022

Summary table of changes

Section Changed	Summary of new information
4.2	Revision to starting dose for Controlled Ovarian Hyperstimulation and Ovulation Induction. Removal of Luteal phase support.
4.3	Removal of lactation as a contraindication
4.4	Paediatric population – removal of reference to 4.3 contraindication section
4.6	Revision of breast feeding text to align with removal of lactation contraindication text from Section 4.3.
4.8	Update to undesirable effects both in the female and male. New Formatting and new tables.
4.9	Correction and update to overdosage section.
5.2	Update to Text consistent with CCDS.
8	Update Sponsor Address details.

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