PRODUCT MONOGRAPH

PUREGON®

(follitropin beta)

Solution for injection in cartridges (recFSH)
300 IU/0.36 mL, 600 IU/0.72 mL or 900 IU/1.08 mL solution for injection

Solution for injection in vials (recFSH)
100 IU/0.5 mL solution for injection

House Standard

Human Gonadotropin

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PUREGON®

(Follitropin beta)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	**Solution in cartridges:** 300 IU/0.36mL, 600 IU/0.72 mL and 900 IU/1.08 mL at a concentration of 833 IU recFSH /mL	Not applicable. *For a complete listing see Dosage Forms, Composition and Packaging section.*
Subcutaneous or Intramuscular injection	**Solution in vials:** 100 IU FSH activity/vial	

INDICATIONS AND CLINICAL USE

In the female:
PUREGON® (follitropin beta) is indicated for:

- Development of multiple follicles in ovulatory patients participating in an Assisted Reproduction Technology (ART) program
- Induction of ovulation and pregnancy in anovulatory infertile females in whom the cause of infertility is functional and not due to primary ovarian failure

In the male:
PUREGON® (follitropin beta) is indicated for:

- Deficient spermatogenesis due to hypogonadotrophic hypogonadism

CONTRAINDICATIONS

For males and females:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Tumours of the ovary, breast, uterus, testis, pituitary gland or hypothalamus.
- A high circulating FSH level indicating primary gonadal failure.

Additionally, PUREGON® (follitropin beta) is contraindicated in females who exhibit:

- uncontrolled thyroid or adrenal dysfunction.
- pregnancy and lactation.
- heavy or irregular vaginal bleeding of undetermined origin.
- ovarian cysts or enlargement not due to polycystic ovary syndrome (PCOS).
- conditions incompatible with pregnancy (e.g. malformation of reproductive organs or fibroid tumours of the uterus).

PUREGON® (follitropin beta) is contraindicated in children.

WARNINGS AND PRECAUTIONS

General

For males and females

PUREGON® (follitropin beta) is a potent gonadotropic agent that is capable of causing severe adverse effects. It should be used only by physicians who are experienced in the management of fertility disorders and only when facilities for appropriate clinical and endocrinologic evaluations are available.

PUREGON® may contain traces of streptomycin and/or neomycin. These antibiotics may cause hypersensitivity reactions in susceptible persons.

Determination of serum gonadotropin concentrations should be obtained to rule out primary gonadal failure.

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

Carcinogenesis and Mutagenesis: PUREGON® displays no mutagenic potential. Carcinogenicity studies have not been performed.

In females

The presence of early pregnancy should be ruled out by a biochemical pregnancy test.

A thorough gynecologic and endocrinologic evaluation must be performed prior to treatment with PUREGON® (follitropin beta). These evaluations may assess uterine and tubal pathology, ovulatory cycle characteristics or an endometrial biopsy. Patients should be evaluated for hypothyroidism, adrenocortical insufficiency, hyperprolactinemia and pituitary or hypothalamic tumours, and appropriate specific treatment given.

Medical conditions that contraindicate pregnancy should be evaluated before starting treatment with PUREGON®.

Evaluation of the fertility potential of the male sexual partner should also be performed (a semen analysis) before starting PUREGON® therapy.

Overstimulation of the Ovary During Therapy:
To minimize the risk associated with abnormal ovarian enlargement in women receiving PUREGON® and human chorionic gonadotropin (hCG) for the induction of ovulation and pregnancy, the drugs should be administered at the lowest possible effective dosage. Since PUREGON® may cause ovarian enlargement and/or hyperstimulation, patients should be assessed for signs of excessive ovarian stimulation during therapy and for a 2-week post-treatment period. Careful monitoring of ovarian response by ultrasound assessment (can minimize the risk of overstimulation. The concurrent determination of serum estradiol levels may also be useful.

Abnormal Ovarian Enlargement: Hemoperitoneum may occur from ruptured ovarian cysts. This is usually the result of sexual intercourse or a vigorous pelvic examination. Should this occur and be accompanied by bleeding to the extent that surgery is necessary, partial resection of the enlarged ovary or ovaries may be required. Intercourse should be prohibited in those patients in whom significant ovarian enlargement occurs after ovulation due to the risk of hemoperitoneum resulting from ruptured ovarian cysts.

Ovarian Hyperstimulation Syndrome: Ovarian Hyperstimulation Syndrome (OHSS) is distinct from uncomplicated ovarian enlargement in that it rarely occurs unless hCG is administered or a pregnancy occurs. Clinical signs and symptoms of mild and moderate OHSS are abdominal pain, nausea, diarrhea, 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, hematological 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.

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.

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. Patients should also be advised not to engage in unprotected sexual intercourse."

OHSS develops rapidly within 3-4 days and generally during the 2-week period following the hCG injection. If OHSS develops, standard and appropriate management of OHSS should be implemented and followed. If severe OHSS occurs, hospitalization may be needed.

Ovarian torsion: Ovarian torsion has been reported after treatment with gonadotropins, including PUREGON®. Ovarian torsion may be associated with other risk factors such as OHSS, pregnancy, previous abdominal surgery, past history of ovarian torsion, previous or current ovarian cyst and polycystic ovaries. Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion.

Liver function test abnormalities: 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.

Cardiovascular:
Thromboembolic events: Thromboembolic events, both in association with and separate from ovarian hyperstimulation syndrome, 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. Complications resulting from thromboembolism have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, stroke, arterial occlusion necessitating limb amputation, and (rarely) death.

In women with generally recognized 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.

Sexual Function/Reproduction:
Multiple Pregnancy: Multiple ovulations with resulting multiple pregnancies and births can occur with 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, preterm birth) outcomes. For anovulatory women undergoing ovulation induction, monitoring follicular development with transvaginal ultrasonography is important for minimizing the risk of multi-fetal gestations. The concurrent determination of serum estradiol levels may also be useful. The patient and her male sexual partner should be informed of the possibility and potential risks associated with 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.

Other Reproductive Complications: Spontaneous abortion rates have been reported from 10 to 25% of all patients following gonadotropin treatment. Increased abortion rates are more common in women over 35 years of age, in women with polycystic ovarian disease, and are more common in the infertile couple. The increased frequency of multiple pregnancy is also associated with an increased rate of abortion.

Infertile women undergoing ART have an increased incidence of ectopic pregnancies. Early ultrasound confirmation that a pregnancy is intrauterine is therefore important.

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple treatment regimens for infertility treatment. It is not established whether or not treatment with gonadotropins increases the risk of these tumours in infertile women.

The incidence of congenital malformations in infants born after ART may be higher than after spontaneous conceptions. This 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. There is no current evidence that the use of gonadotropins during ART is associated with an increased risk of congenital malformations.

In males

Evaluation of the fertility potential of the male sexual partner should also be performed (a semen analysis) before starting PUREGON® therapy.

Patients should be evaluated for hypothyroidism, adrenocortical insufficiency, hyperprolactinemia and pituitary or hypothalamic tumors, and appropriate specific treatment given.

Elevated endogenous FSH levels in men are indicative of primary testicular failure. Such patients are unresponsive to PUREGON®/hCG therapy.

Special Populations

Pregnant Women: PUREGON® is not intended for use during pregnancy.

In case of inadvertent exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of recombinant FSH.

Nursing Women: PUREGON® is not intended for use during lactation.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

The following adverse events, listed by body system, have been reported in clinical studies evaluating the efficacy and safety of PUREGON® (follitropin beta) in women.

% Incidence of Most Frequently (≥1%) Reported Adverse Events (AEs) in Clinical Trials		
Body System	PUREGON® (n=1074)	Urinary gonadotropin (n=498)
	%	
Patients with at least one AE	17.3	19.7
Patients with known severe AE	5.0	6.2
Patients with drug-related AEs †	8.7	8.2
Reproductive System *Ovarian hyperstimulation syndrome* *Ectopic pregnancy* *Vaginal hemorrhage*	8.8 5.0 2.1 1.0	9.4 4.0 3.4 1.0
Gastrointestinal System *Abdominal pain*	3.6 2.0	4.2 2.4
Fetal Disorders *Miscarriage*	3.1 3.1	4.2 4.2
Body as a Whole	1.2	1.0
Application Site Disorders *Injection site pain*	1 1	0.6 0.6
Hearing/Vestibular Disorders	0	0.2

† Related: definitely, probably, or possibly related to the study drug

% Incidence of Most Frequently (< 1%) Reported Adverse Events (AEs) in Clinical Trials		
Body System	PUREGON® (n=1074)	Urinary gonadotropin (n=498)
	%	
Reproductive System *Vaginitis*	 0.4	 0.2
Gastrointestinal System *Abdominal pain - upper/lower* *Nausea* *Abdominal discomfort*	 0.7 0.5 0.4	 0.6 0.8 0.2
Urinary System *Urinary tract infection*	0.8 0.5	0.4 0.2
Neoplasms *Ovarian cyst*	0.8 0.7	0.8 0.8
Central and Peripheral Nervous System *Headache*	0.7 0.7	0.6 0.4
Resistance Mechanism Disorders	0.5	0.2
Skin and Appendages	0.4	0.6
Autonomous Nervous System (hyperemesis, loose stools, vasovagal syncope)	0.4	0
Respiratory System (dyspnea, rhinitis, sore throat, upper respiratory tract infection)	0.4	0.6
Platelet/ Bleeding, Clotting Disorders	0.2	0
Psychiatric Disorders (Nervousness)	0.1	0
Vision/Eye Abnormalities	0.1	0.2
Hearing/Vestibular Disorders	0	0.2

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Reproductive Disorder Women: Premature labour, menorrhagia, ovarian disorder, vaginal discharge, vulvovaginitis, genital infection, genital herpes.

Skin and Appendages: Eczema, itching, rash, hematoma, abscess, Herpes zoster.

Respiratory System: Dyspnea, otitis media

Gastrointestinal: Bloating, constipation, gastroesophageal reflux, vomiting, increased bilirubin, swollen abdomen.

Urinary System: Dysuria**,** cystitis, frequent micturition.

Body as a Whole, General Disorders: Back pain, feeling unwell, influenza-like symptoms,face edema, lumbar pain, pain, sepsis, tooth disorder, hydatidiform mole
Autonomous Nervous System: Hypermesis, hot flashes, syncope

Abnormal Hematologic and Clinical Chemistry Findings
Post-treatment sera were analysed following three treatment cycles and no evidence of induction of anti-FSH or anti-CHO cell-derived protein antibodies were found.

In Males:
The safety of PUREGON® was examined in a clinical trial that enrolled 49 male patients for the indication of spermatogenesis, of whom 30 received PUREGON®. Two subjects in the treatment period each reported one serious event, which were judged not related to study drug by the investigator. The events involved are pilonidal cyst and hemorrhoids. Both subjects recovered from these adverse events. In the PUREGON® treatment phase, no patients discontinued due to an adverse event.

In total, 21 patients in the treatment phase experienced at least one adverse event. Ten were reported by the investigator to be possibly related to study drug. These include: two cases of acne, two cases of injection site bruising, two cases of injection site pain, and single cases of varicose veins, gynecomastia, injection site induration, and dermoid cyst.

Number (%) of Male Subjects with at least one AE per MedDRA Body System and Preferred term Trials: P37618 (male trial)

Reported Adverse Drug Reactions in Clinical Trials with Incidence of > 1%		
MedDRA System Organ Class MedDRA Preferred term	Treatment Group PUREGON® N=30	
	All n (%)	Drug related n (%)
Blood and lymphatic system disorders		
Leukopenia	1 (3.3)	0 (0.0)
Lymphadenopathy	1 (3.3)	0 (0.0)
Neutropenia	1 (3.3)	0 (0.0)
Gastrointestinal disorders		
Haemorrhoids	1 (3.3)	0 (0.0)
General disorders and administration site conditions		
Injection site bruising	2 (6.7)	2 (6.7)
Injection site haemorrhage	1 (3.3)	0 (0.0)
Injection site induration	1 (3.3)	1 (3.3)
Injection site pain	2 (6.7)	2 (6.7)
Pyrexia	2 (6.7)	0 (0.0)
Infections and infestations		
Bronchitis	1 (3.3)	0 (0.0)
Influenza	5 (16.7)	0 (0.0)
Nasopharyngitis	1 (3.3)	0 (0.0)
Pilonidal cyst	1 (3.3)	0 (0.0)

Viral infection	2 (6.7)	0 (0.0)
Injury, poisoning and procedural complications		
Upper limb fracture	1 (3.3)	0 (0.0)
Investigations		
Aspartate aminotransferase increased	1 (3.3)	0 (0.0)
Blood lactate dehydrogenase increased	1 (3.3)	0 (0.0)
Blood urea increased	1 (3.3)	0 (0.0)
Red blood cells semen positive	1 (3.3)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Back pain	2 (6.7)	0 (0.0)
Nervous system disorders		
Headache	2 (6.7)	0 (0.0)
Reproductive system and breast disorders		
Epididymal cyst	1 (3.3)	1 (3.3)
Gynecomastia	1 (3.3)	1 (3.3)
Varicocele	1 (3.3)	1 (3.3)
Respiratory, thoracic and mediastinal disorders		
Cough	1 (3.3)	0 (0.0)
Pharyngolaryngeal pain	1 (3.3)	0 (0.0)
Skin and subcutaneous tissue disorders		
Acne	2 (6.7)	2 (6.7)
Rash	1 (3.3)	0 (0.0)

Note: Coded with MedDRA version 8.1

Post-Market Adverse Drug Reactions

Post-Market Clinical Trials:

Clinical use of PUREGON® 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. Generalized hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.2% of all patients treated with PUREGON®).

Treatment of females

In approximately 4% of the women treated with PUREGON® in clinical trials, signs and symptoms related to ovarian hyperstimulation syndrome (OHSS) have been reported. Undesirable effects related to this syndrome include pelvic pain and/or congestion, abdominal pain and/or distension, breast complaints (breast tenderness, pain and/or engorgement, nipple pain), ovarian enlargement, and spontaneous abortion.

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.

Number (%) of Female Subjects with at least one AE per MedDRA Body System and Preferred term Trials: all female studies (Europe, US and Japan)

Reported Adverse Drug Reactions in Clinical Trials with Incidence of > 1%		
MedDRA System Organ Class MedDRA Preferred term	Treatment Group	
	PUREGON®	
	N=3535	
	All n (%)	Drug related n (%)
Gastrointestinal disorders		
Abdominal distension	42 (1.2)	38 (1.1)
Abdominal pain	43 (1.2)	19 (0.5)
Nausea	44 (1.2)	19 (0.5)
General disorders and administration site conditions		
Injection site pain	71 (2.0)	68 (1.9)
Nervous system disorders		
Headache	96 (2.7)	37 (1.0)
Pregnancy, puerperium and perinatal conditions		
Abortion spontaneous	113 (3.2)	24 (0.7)
Ectopic pregnancy	44 (1.2)	7 (0.2)
Reproductive system and breast disorders		
Ovarian hyperstimulation syndrome	138 (3.9)	129 (3.6)
Pelvic pain	67 (1.9)	44 (1.2)

Note: Coded with MedDRA version 8.1

Less Common Adverse Drug Reactions reported in post-market clinical trials (<1%)

Gastrointestinal disorders:

Abdominal discomfort, constipation, diarrhea.

Reproductive system and breast disorders:

Metrorrhagia, ovarian cyst, ovarian torsion, uterine enlargement, vaginal hemorrhage.

Post-market reports

Adverse reactions identified during post-marketing surveillance were consistent with those reported in clinical trials.

In women:

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

DRUG INTERACTIONS

Overview

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

PUREGON® may be given alone, or in combination with clomiphene citrate to stimulate the endogenous production of gonadotropins or in combination with a GnRH agonist to prevent premature luteinisation (see DRUG INTERACTIONS).

Recommended Dose and Dosage Adjustment

Dosage:

In the Female:

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.

In comparative clinical studies with PUREGON® and urinary FSH it was shown that PUREGON® is more effective than urinary FSH in terms of a lower total dose and a shorter treatment period needed to achieve pre-ovulatory conditions. Therefore, it is considered appropriate to give a lower dosage of PUREGON® than generally used for urinary FSH, not only in order to optimize follicular development but also to reduce the risk of unwanted ovarian hyperstimulation.

After pituitary desensitization induced by GnRH agonist a higher dose of PUREGON® may be necessary to achieve an adequate follicular response. Clinical experience with PUREGON® is based on up to three treatment cycles in both indications. Overall experience with IVF indicates that in general the treatment success rate remains stable during the first four attempts and gradually declines thereafter.

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

discontinued and ovulation can be induced by administering human chorionic gonadotropin (hCG).

If the number of responding follicles is too high or estradiol levels increase too rapidly, i.e. more than a daily doubling for estradiol for 2 or 3 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:
The dosage regimen may vary according to the physician's preference or the patient's response. In general, stimulation of follicular growth is achieved by starting with daily s.c. or i.m (see Administration) administration of 150-225 IU PUREGON® for a period of 4 days. Thereafter, the dose may be adjusted according to the individual's ovarian response.

Maturation of follicles is monitored by pelvic ultrasound assessment. The concurrent determination of serum estradiol levels may also be useful. In responding patients, daily maintenance doses of 75 to 300 IU for 6 to 12 days are usually sufficient, although longer treatment may be necessary. The maximum individualized daily dose safely used in clinical studies was 450 IU. There is limited experience with higher doses. When ultrasonic evaluation indicates the presence of at least three follicles of sufficient size and there is evidence of a good estradiol response, the final phase of maturation of the follicles is induced by administration of hCG. HCG is given 30-40 hours after the last administration of PUREGON® in a dose of 5000-10000 IU

After embryo transfer, up to three repeat injections of 1000 to 3000 IU hCG each, may be given within the following 9 days to provide luteal phase support.

Dosage in the Male:
PUREGON® should be given at a dosage of 450 IU/week, preferably divided in 3 dosages of 150 IU (two doses of 225 IU per week is considered to be equivalent) concomitantly with hCG. Please note that the intramuscular route of administration of PUREGON® in males has not been evaluated. Treatment with PUREGON® and hCG should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. To assess the response, semen analysis is recommended 4 to 6 months after the beginning of treatment. If a patient has not responded after this period, the combination therapy may be continued. The efficacy and safety of PUREGON® have not been established beyond a treatment period of 48 weeks. Clinical experience with other gonadotropins suggests that treatment for up to 18 months or longer may be necessary to achieve spermatogenesis.

Administration:
PUREGON® (follitropin beta) solution for injection in cartridges:
PUREGON® (follitropin beta) solution for injection in cartridges has been developed for use with the PUREGON PEN® (a pen-injector) and should be administered subcutaneously. The injection site should be alternated to prevent lipoatrophy.

When using the pen-injector, it should be realized 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. Since the daily dose of PUREGON® is determined by the patient's individual ovarian response, the slightly higher dose delivered by the PUREGON PEN® is unlikely to affect clinical outcome. It may however be of relevance when switching between the pen-injector and a conventional syringe within one treatment cycle. Especially when switching from a syringe to the PUREGON PEN®, small dose adjustments may be needed to prevent too high of a dose being given.

In view of loss of the active ingredient because of priming and dead volume, the 300 IU/0.36 mL cartridge contains a minimum of 400 IU / 0.48mL which is sufficient for a net deliverable dose of 300 IU The 600 IU/0.72 mL cartridge contains a minimum of 700 IU / 0.84mL which is sufficient for a net deliverable dose of 600 IU and the 900 IU/1.08 mL cartridge contains a minimum of 1025 IU / 1.23mL which is sufficient for a net deliverable dose of 900 IU

The net deliverable dose of 300 IU, 600 IU and 900 IU are based upon a maximum of six 50 IU injections, six 100 IU injections and nine 100 IU injections respectively.

When more injections are given, the net total dose of active ingredient may be lowered, because each injection has to be preceded by an air shot.

The instructions for using the pen must be followed carefully.

PUREGON® (follitropin beta) Solution for Injection in vials:

Administer the PUREGON® solution either subcutaneously or intramuscularly**.** Any unused solution should be discarded.

Subcutaneous Administration

The best site for subcutaneous injection is in the abdomen around the navel (an alternate site is the upper thigh). Pinch up a large area of skin between the finger and thumb. Vary the injection site with each injection. The needle should be inserted at a 90° angle to the skin surface. The first injection of PUREGON® should be performed under direct medical supervision. Subcutaneous administration of PUREGON® can be carried out by the patients or by their partners, provided that proper instructions are given by the physician. Self-administration of PUREGON® should only be performed by patients who are well motivated, adequately trained and with access to expert advice.

Intramuscular Administration

The best site for intramuscular administration is the upper outer quadrant of the buttock muscle. Stretching the skin helps the needle to go in more easily and pushes the tissue beneath the skin out of the way. This helps the solution to disperse correctly. The needle should be inserted right up to the hilt at an angle of 90° to the skin surface. Inserting the needle with a quick thrust causes the least discomfort.

OVERDOSAGE

The acute toxicity of gonadotropin preparations has been shown to be very low. However, too high a dosage for more than one day may lead to hyperstimulation of the ovaries (see WARNINGS AND PRECAUTIONS).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

Pharmacodynamics

PUREGON® (follitropin beta) is a sterile solution containing highly purified human follicle-stimulating hormone (hFSH) prepared by recombinant DNA technology. The active substance, follitropin beta, is a heterodimeric glycoprotein with a molecular mass of approximately 35-45kD. It is produced by a Chinese hamster ovary (CHO) cell line transfected with a plasmid containing two subunit genes encoding human FSH. Structural analysis has shown that the amino acid sequence of follitropin beta is identical to that of natural hFSH. The oligosaccharide side chains are very similar to those reported for natural hFSH but not completely identical. These small differences do not affect the degree of charge heterogeneity, receptor binding affinity and bioactivity of follitropin relative to natural hFSH. Follitropin beta, as purified from the CHO cell culture supernatant, is of high biochemical purity ($\geq$ 99%), high specific biological activity (approximately 10,000 IU/mg protein), and devoid of luteinizing hormone (LH) activity.

Follicle-stimulating Hormone (FSH) is essential for normal female and male gamete growth and maturation, and gonadal steroid production. Deficiencies in the endogenous production of FSH may lead to infertility.

FSH is critical for the onset and duration of follicular development, and consequently for the timing and number of follicles reaching maturity in females. The primary action of follitropin beta in women with gonadal dysfunction, is the stimulation of follicular development and steroid production. Follitropin may also be used to promote multiple follicular development in medically assisted reproduction programs (i.e. IVF/ET/ISCI) and gamete or zygote intra-fallopian transfer (GIFT/ZIFT). In order to induce ovulation, in the absence of an endogenous LH surge, human chorionic gonadotropin (hCG) must be given after follitropin beta administration once follicular maturation has occurred.

Pharmacokinetics

	C_{max} (IU/L)[1]	$t_{1/2}$(h)[2]	AUC_{0-oo} (IU• h/L)[1]	Clearance (L/h)[1] (intravenous)	Volume of distribution (L)[3]
Single dose mean	SC: 5.4 IM: 6.9	34	SC: 456 IM: 446	0.51	25

[1] taken from trial 37614 (n=13)

[2] taken from trial 37626 (n=22)

[3] volume of distribution during terminal phase calculated as CL

Absorption:

After i.m. or s.c. administration of follitropin beta, high concentrations of FSH are reached within about 12 hours. After intramuscular administration of PUREGON®, the maximum FSH concentrations are higher and reached earlier in men as compared to women. FSH levels remain high for 24-48 hours due to follitropin beta's relatively long elimination half-life of about 40 hours (ranging from 12 to 70 hours). Plasma FSH concentrations, after repeated administration of PUREGON®, are approximately 1.5 - 2.5 times higher than after single dose administration.

The bioavailability of PUREGON® following subcutaneous and intramuscular administration was investigated in healthy, pituitary-suppressed, female subjects given a single 300 IU dose. After subcutaneous or intramuscular injection the apparent dose absorbed was 77.8% and 76.4%, respectively.

The subcutaneous (455.6 ± 141.4 IU· h/L) and intramuscular (455.7 ± 135.7 IU· h/L) routes of administration were equivalent with respect area under the curve (AUC) in healthy, pituitary-suppressed, female subjects given a single 300 IU dose. However, equivalence could not be established for C_{max} between the subcutaneous (5.41 ± 0.72 IU/L) and intramuscular (6.86 ± 2.90 IU/L) routes of administration.

The pharmacokinetics and pharmacodynamics of a single, intramuscular dose (300 IU) of PUREGON® were also investigated in a group of gonadotropin-deficient, but otherwise healthy women. Peak (C_{max}) serum FSH levels in these women were 4.3 ± 1.7 IU/L (mean ± SD) and they occurred approximately 27 hours after intramuscular administration.

A multiple, dose proportionality, pharmacokinetic study of PUREGON® was completed in healthy, pituitary-suppressed, female subjects given intramuscular doses of 75 IU, 150 IU or 225 IU for 7 days. Steady–state blood concentrations of FSH were reached with all the doses after 4 days of treatment based on the minimum concentrations of FSH just prior to dosing (C_{min}). Peak blood concentrations with the 75IU, 150 IU, and 225 IU dose were 4.65 ± 1.49 IU/L, 9.46 ± 2.57 IU/L and 11.30 ± 1.77 IU/L, respectively.

A multiple, dose proportionality, pharmacokinetic study of PUREGON® was completed in healthy, pituitary-suppressed, female subjects given subcutaneous doses of 75 IU, 150 IU, or 225 IU for 7 days. Steady–state blood concentrations of FSH were reached with all the doses after 5 days of treatment based on the minimum concentrations of FSH just prior to dosing (C_{min}). Peak blood concentrations with the 75 IU, 150 IU, and 225 IU dose were 4.30 ± 0.60 IU/L, 8.51 ± 1.16 IU/L and 13.92 ± 1.81 IU/L, respectively.

Distribution:
The volume of distribution of PUREGON® in healthy, pituitary-suppressed, female subjects following intravenous administration of 300IU dose was approximately 8L.

Metabolism:
The recombinant FSH in PUREGON® is biochemically very similar to urinary FSH and it is therefore anticipated that it is metabolized in the same manner.

Excretion:
The elimination half-life following a single intramuscular dose (300 IU) of PUREGON® in female subjects was 43.9 ± 14.1 hours (mean ± SD). The elimination half–life following a 7-day

intramuscular treatment with 75 IU, 150 IU or 225 IU was 26.9 ± 7.8 hours (mean ± SD), 30.1 ± 6.2 hours (mean ± SD) and 28.9 ± 6.5, respectively.

There are no significant pharmacokinetic differences between intramuscular and subcutaneous administration of PUREGON®. Both have an absolute bioavailability of approximately 77%. Recombinant FSH is biochemically very similar to urinary human FSH and is distributed, metabolized, and excreted in the same way.

Special Populations and Conditions

No studies have been conducted with special populations and conditions.

STORAGE AND STABILITY

Pharmacist: Store in a refrigerator (2 ºC - 8ºC). Keep the vial(s)/cartridge(s) in the outer carton. Do not freeze. Protect from light.

Patient: Store in a refrigerator (2 ºC - 8ºC) **or** store at or below 25ºC for a maximum of 3 months. Keep the vial(s)/cartridge(s) in the outer carton. Do not use past expiry date. Protect from light.

PUREGON® Solution for Injection in Cartridges:
Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days.

PUREGON® Solution for Injection in Vials:
The contents of a vial should be used immediately after piercing of the rubber stopper.

Route of Administration

PUREGON® Solution for Injection in Cartridge:
For subcutaneous injection only.

PUREGON® Solution for Injection in Vials:
For intramuscular or subcutaneous injection. For single use only. Once solution has been taken from a vial, any unused drug (solution) should be discarded.

SPECIAL HANDLING INSTRUCTIONS

The instructions for the pen must be followed carefully (see PUREGON PEN® booklet).

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

Composition of Solution for Injection in Cartridges:
Solution for injection in cartridges - 833 IU/mL. Cartridges contain a minimum of 400 IU FSH activity in 0.48 mL aqueous solution which is sufficient for a net deliverable dose of 300 IU, a minimum of 700 IU FSH activity in 0.84 mL aqueous solution which is sufficient for a net deliverable dose of 600 IU or a minimum of 1025 IU FSH activity in 1.23mL which is sufficient for a net dose of 900 IU.

The net deliverable dose of 300 IU, 600 IU and 900 IU are based upon a maximum of six 50 IU injections, six 100 IU injections and nine 100 IU injections respectively.

When more injections are given, the net total dose may be lowered because each injection has to be preceded by an air shot.

	300 IU Cartridge (Net deliverable dose[1]) per cartridge
Follitropin beta (recFSH)	350 IU
Volume of solution	0.420mL[2]
Sucrose	21.0 mg
Sodium citrate.2 aq	6.17 mg
Polysorbate 20	0.084 mg
L-Methionine	0.21 mg
Hydrochloric acid 0.1N	trace amounts for pH adjustment to pH 7.0
Sodium hydroxide 0.1N	trace amounts for pH adjustment to pH 7.0
Benzyl alcohol (as preservative)	4.2 mg
Concentration recFSH	833 IU/mL

	600 IU Cartridge (Net deliverable dose)[1] per cartridge	**900 IU Cartridge (Net deliverable dose)[1] per cartridge**
Follitropin beta (recFSH)	650 IU	975 IU
Volume of solution	0.780 mL[2]	1.170 mL[2]
Sucrose	39.0 mg	58.5 mg
Sodium citrate.2 aq	11.5 mg	17.2 mg
Polysorbate 20	0.156 mg	0.234 mg
L-Methionine	0.39 mg	0.59 mg
Hydrochloric acid 0.1N	trace amounts for pH adjustment to pH 7.0	
Sodium hydroxide 0.1N	trace amounts for pH adjustment to pH 7.0	
Benzyl alcohol (as preservative)	7.8 mg	11.7 mg
Concentration recFSH	833 IU/mL	833 IU/mL

[1]Including the amount for priming
[2]Extractable volume (overfill at least 0.06 mL)

Composition of Solution for Injection in vials:

Solution for injection	100 IU FSH activity/0.5 mL
Follitropin beta (recFSH)	100 IU / vial
Sucrose	25.0 mg
Sodium citrate, dihydrate	7.35 mg
Polysorbate 20	0.1 mg
L-Methionine	0.25 mg
Hydrochloric acid 0.1N	trace amounts for pH adjustment
Sodium hydroxide 0.1N	trace amounts for pH adjustment

Packaging:

PUREGON® (follitropin beta) solution for injection in cartridges:
Boxes of PUREGON® solution for injection contain 1 cartridge of PUREGON® and 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.

Cartridges contain 833 IU of FSH activity per mL aqueous solution. Cartridges with a net dose 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 1025 IU in 1.230 mL.

PUREGON® (follitropin beta) solution for injection in vials:
Boxes of PUREGON® solution for injection contain 1, 5 or 10 vial(s) of PUREGON® in 0.5 mL aqueous solution. PUREGON® solution for injection is filled in colourless, 3 mL vials of hydrolytic resistant glass, Type 1, and closed with chlorobutyl rubber closures.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Follitropin beta

Chemical name: Recombinant follicle-stimulating hormone (recFSH)

Molecular formula: Not applicable

Molecular mass: Approximately 35-45 kD

Structural formula: Not applicable

Physicochemical properties: White to off-white cake or powder

pH: 6.5 to 8.5

CLINICAL TRIALS

Ovulation Induction

The efficacy and safety of PUREGON® (follitropin beta) and urinary gonadotropin were evaluated in patients with chronic anovulation (WHO group II) who failed to ovulate and/or conceive during clomiphene citrate treatment. With PUREGON®, ovulation was achieved with a significantly fewer number of ampoules and within a shorter treatment period, indicating a higher efficiency in ovulation induction. The higher efficiency of PUREGON® and the fact that a greater number of follicles of □12 mm were found suggest that PUREGON® treatment may be started at a lower dose than urinary gonadotropin and maintained at this lower dose for a longer period of time.

Mean Results on Efficacy and Efficiency Parameters			
Parameter	**PUREGON® (i.m.)**	**Urinary gonadotropin (i.m.)**	**p value**
First cycle (adjusted for centre)	n=105	n=67	
Number of ampoules/vials	12.8	19.8	p<0.01
Treatment length (days)	12.0	16.2	p<0.01
Number of follicles□12 mm	2.93	1.91	p<0.01
Number of follicles□15 mm	2.0	1.7	nd
Number of follicles□ 18 mm	1.1	0.9	nd
Serum estradiol on day of hCG(pmol/L)	1763	1138	nd
Second cycle (unadjusted for centre)			
Number of ampoules/vials	12.5	27.4	nd
Treatment length (days)	11.4	19.4	nd
Number of follicles□12 mm	3.6	3.0	nd
Number of follicles□15 mm	2.0	1.6	nd
Number of follicles□ 18 mm	1.1	1.0	nd
Serum estradiol on day of hCG(pmol/L)	1837	1314	nd
Third cycle (unadjusted for centre)			
Number of ampoules/vials	11.6	15.2	nd
Treatment length (days)	11.3	12.9	nd
Number of follicles□12 mm	3.8	2.1	nd
Number of follicles□15 mm	2.6	1.4	nd
Number of follicles□ 18 mm	1.3	0.7	nd
Serum estradiol on day of hCG(pmol/L)	2461	1228	nd

nd: not determined

Controlled Ovarian Hyperstimulation in Assisted Reproduction Programs

The efficacy and safety of PUREGON® (follitropin beta) was assessed and compared to urinary gonadotropin in infertile pituitary-suppressed subjects undergoing ovarian hyperstimulation followed by in vitro fertilization (IVF) and embryo transfer (ET). The study was designed as a randomized, assessor-blind, group-comparative trial of 1027 subjects randomized to PUREGON® or urinary gonadotropin treatment in a 3:2 ratio.

Statistical analysis showed that the PUREGON® group required significantly ($p<0.01$) fewer ampoules/vials of FSH (mean 28.5) than the urinary gonadotropin group (mean 31.8), and a shorter period of treatment (10.7 vs 11.3 days).

	Means Adjusted for Centre		Treatment Differences	
	PUREGON® (n=546)	**Urinary gonadotropin (n=361)**	**Estimate of difference**	**95% conf. interval (p-value)**
Number of ampoules/vials Duration of treatment (days)	28.5 10.7	31.8 11.3	-3.3 -0.6	-4.5 to -2.1 (<0.01) -0.9 to -0.3 (<0.01)
Follicles ≥ 15mm Follicles ≥ 17 mm Maximal serum estradiol (pmol/L)	7.5 4.6 6084	6.7 4.4 5179	0.8 0.2 905	0.4 to 1.2 (<0.01) -0.0 to 0.5 (= 0.09) 494 to 1317 (<0.01)
Total number of oocytes Number of mature oocytes Number of type 1 and 2 embryos	10.8 8.6 3.1	9.0 6.8 2.6	1.9 1.8 0.5	1.2 to 2.6 (<0.01) 1.1 to 2.4 (<0.01) 0.2 to 0.8 (= 0.01)

Both treatment groups were similar with respect to the number of follicles with a diameter of over 17 mm. However, there was a significantly greater number of follicles of 15 mm (7.5 for PUREGON® and 6.7 for urinary gonadotropin, respectively, ($p<0.01$)). In addition, the mean maximum serum estradiol concentration was significantly higher in the PUREGON® group [6084 vs 5179 pmol/L, ($p<0.01$)].

In 11 out of the 18 centres contributing to the analysis of plasma FSH, the mean immunoreactive FSH concentration just before, or on the day of human chorionic gonadotropin (hCG) administration was significantly higher in the urinary gonadotropin group than in the PUREGON® group (12.1 vs 11.5 IU/L, $p=0.03$). However, the mean total number of oocytes per aspiration was consistently and significantly higher in the PUREGON® group (difference of 1.8 oocytes, $p<0.01$).

Although the median fertilization rates were similar in the PUREGON® and urinary gonadotropin groups (64.7 and 62.5 %, respectively), a significantly higher ($p=0.01$) mean number of high-quality (type 1 and type 2) embryos were found in the PUREGON® group.

The two treatment groups had a similar percentage of transfers (85.5% vs 83.1% in the PUREGON® and urinary gonadotropin group, respectively), with a similar mean number of embryos (2.4 for both groups).

The treatment cycle outcome and the mean ongoing pregnancy rates (single and multiple vital pregnancies), all expressed per attempt and per embryo transfer, are shown in the following tables:

	Per Attempt (%)		Per Transfer (%)	
Treatment cycle outcome	**PUREGON®**	**Urinary gonadotropin**	**PUREGON®**	**Urinary gonadotropin**
No transfer	14.5	16.9	-	-
No pregnancy after embryo transfer	54.9	56.1	64.2	67.5
Miscarriage without proof of vital fetus	5.1	5.3	6	6.4
Miscarriage after proof of vital fetus	1.9	1.8	2.2	2.1
Ectopic pregnancy	1.5	1.8	1.8	2.1
Single vital pregnancy	14.9	10.9	17.4	13.7
Multiple vital pregnancy	7.2	7.3	8.4	8.2

Pregnancies	**Treatment Group**	**Mean Ongoing Pregnancy Rates Adjusted for Centre (%)**	**Treatment differences**	
			Estimate of Difference	**95% Conf. Interval (p-value)**
Per attempt	PUREGON® (n=585) Urinary gonadotropin (n=396)	22.2 18.2	4	-1.1 to 9.0 (0.1)
Per embryo transfer	PUREGON® (n=500) Urinary gonadotropin (n=329)	26.0 22.0	4	-1.9 to 9.8 (0.2)

A slight, although not significant, difference in pregnancy rates in favour of the PUREGON® group (about 4%) was found. The cumulative pregnancy rate after the first FSH treatment cycle, including frozen embryo cycles, showed a 5.3% difference (p=0.05) in favour of PUREGON®-treated women. Results of pregnancy follow-up after the first treatment cycle, showed no statistically significant differences between the two agents. Similarly, the rate of complications during pregnancy and delivery, as well as the incidence of congenital malformations, were comparable for the two treatment groups and were not increased compared to data on routine obstetrical practice. Follow-up of children, evaluated in two studies (one year follow-up and 4-8 week follow-up, respectively) did not reveal any unexpected abnormalities and psychomotor development was normal in all children.

Data from two additional studies confirmed the superior efficacy of PUREGON® compared with urinary gonadotropin in inducing oocyte production with a fewer number of ampoules and over shorter periods of time.

Male Infertility:

Initiation / Restoration of Spermatogenisis in Hypogonadotropic Hypogonadal Men

The efficacy and safety of PUREGON® was assessed in hypogonadotropic hypogonadal male subjects. The study was designed as an open-label, multi-centre, efficacy and safety trial and consisted of a pre-treatment phase and treatment phase. In the pre-treatment phase subjects were treated with hCG (1500 IU, twice weekly) for 16 weeks to normalize the testosterone levels. In the treatment phase, 30 subjects received both hCG and PUREGON® for a period of 48 weeks. The subjects were randomized in two groups and received either 150 IU PUREGON® three times per week or 225 IU two times a week, both amounting to a total dose of 450 IU.

The average success rate (mean sperm concentration of ≥ 10^6 / mL over the last two assessments) was 43% in the 150 IU PUREGON® (three times a week) and 44% in the 225 IU PUREGON® (two times a week) groups, respectively. If data were analyzed according to the actually followed treatment these figures were comparable (40% and 47% respectively).

A total of fourteen subjects (47%) demonstrated a sperm concentration of at least 1 million/mL during treatment. This was achieved at a median time of 165 days, ranging from 25 to 327 days. In 20 subjects (67%) receiving combination therapy, sperm appeared in the ejaculate. The percentage of morphologically normal sperm cells remained fairly constant over the whole treatment period as well as the percentage of highly motile sperm cells. For most parameters, slightly better results were obtained in the 225 IU treatment group in comparison with the 150 IU group. This may be due to a difference in subject population as reflected by higher initial testicular volume in the 225 IU treatment group. A higher testicular volume is generally regarded as a prognostic factor for positive treatment outcome in male infertility. However, in view of the small number of subject's pre-treatment group, this may also be due to chance. Overall, the observed difference is not considered to be clinically relevant.

With respect to local tolerance no major differences were observed between the two treatment groups. Antibodies against FSH or CHO cell-derived proteins were not present.

DETAILED PHARMACOLOGY

Follitropin beta, the active ingredient in PUREGON® (follitropin beta) prepared by recombinant DNA technology, is highly pure (≥99%), of high specific bioactivity (approximately 10 000 IU/mg protein) and devoid of LH activity. It caused no clinically significant toxic effects when administered to animals in pre-clinical studies.

In vitro studies

The receptor-binding affinity displayed by follitropin beta was similar to that of urinary gonadotropin preparations. Aromatase induction in Sertoli and granulosa cells, in terms of dose-dependency and maximal responses, was comparable to urinary gonadotropin preparations. A similar pattern of inhibition of induced aromatase activity by specific monoclonal antibodies confirmed the structural and functional similarity between follitropin beta and urinary gonadotropin preparations. No relevant intrinsic LH bioactivity was measured in a Leydig cell assay. The isohormone distribution of follitropin beta, ranging between pI values of 5.7 and 3.2, was slightly more basic than that of urinary FSH.

In vivo studies
In the standard ovarian weight augmentation assay follitropin beta displayed a specific bioactivity of about 10 000 IU/mg protein. In hypophysectomized rats follitropin beta was effective in increasing ovarian weight and aromatase activity, without increasing plasma estradiol levels. Follitropin beta caused a gradual shift from small antral to large pre-ovulatory follicles and reduced the number of atretic follicles in a dose-dependent way. Co-administration of hCG was required to make follitropin beta effective in the elevation of plasma estradiol levels. The capability of follitropin beta to increase ovarian weight and plasma estradiol levels compared well to those of urinary preparations, when it was supplemented with the proper quantities of hCG.

Follitropin beta induced pro-oestrus in rats and dogs.

When given as a single i.v. dose to anaesthetized dogs or as a repeated i.m. dose to conscious rabbit's follitropin beta induced no significant cardiovascular or haemodynamic effects.

Pharmacokinetics
The pharmacokinetic behaviour of follitropin beta in the rat is essentially similar to that of urinary gonadotropins, all parameters being compared on the basis of the immunoreactive FSH plasma concentrations after the administration of the same dose in terms of *in vivo* bioactivity. The kidney plays a major role in the removal of follitropin beta from the circulation.
In dogs (i.v.) and in man (i.m.), follitropin beta was found to have a somewhat lower AUC than urinary gonadotropin after single-dose administration.

On repeated i.m. dosing no significant differences were observed. This is likely due to the fact that the basic isohormones, which are more prevalent in follitropin beta, do not contribute or contribute very little to the steady-state plasma concentrations.

As shown by the single-dose i.v. study in dogs comparing three different batches of follitropin beta, variations in the isohormone profile [more or less acidic, corresponding to a higher or lower B (*in vitro*)/I ratio, respectively] do not lead to different AUCs.

Both in dogs and in man, the rate and extent of absorption were the same after i.m. and s.c. administration.

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 x 75 IU) versus administration of PUREGON® ready-for-use solution (150 IU) with pen-injector. After correction of the dose by a factor of 1.18, bioequivalence was demonstrated for all relevant pharmacokinetic parameters. Since the daily dose of PUREGON® is determined by the patient's individual ovarian response, the slightly higher dose delivered by the PUREGON PEN® is unlikely to affect clinical outcome.

MICROBIOLOGY
Not applicable

TOXICOLOGY

Single dose i.v. and i.m. administration of follitropin beta to intact rats caused no drug-related toxicological effects.

Follitropin beta when given i.m. as a repeated daily dose for 2 weeks up to 100-fold the anticipated maximal daily human dose induced no toxicologically significant effects.

In Ames tests using *Escherichia coli* and *Salmonella typhimurium* strains PUREGON® showed no mutagenic potential.

After a single i.v. injection of follitropin beta in rats no anti-recFSH antibodies were observed. However, anti-recFSH antibodies were induced in a single rat within 4 days and in the majority of rats after 7 days of i.m. administration of 500 IU/kg follitropin beta. After 2 weeks, all rats dosed at 50 or 500 IU/kg were positive for the presence of anti-recFSH antibodies. A higher titre of antibodies occurred at earlier stages in the female rats.

No anti-recFSH antibody formation was seen in dogs.

Treatment of human subjects, for up to 3 cycles, did not result in the formation of anti-recFSH or anti-CHO cell-derived protein antibodies.

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PART III: CONSUMER INFORMATION

PUREGON®
(follitropin beta)

This leaflet is part III of a three-part "Product Monograph" published when PUREGON® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PUREGON®. Contact you doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

The name of your medicine is PUREGON®. It contains follicle-stimulating hormone (FSH) in a solution in a cartridge, corresponding to 300, 600 or 900 international units (IU) net total dose per cartridge or solution for injection 100 international units (IU) per vial. PUREGON® is produced by mammalian cells, which by recombinant DNA technology were changed to carry the genes for human FSH.

PUREGON® belongs to a group of medicines called "gonadotropins".

What it does:

PUREGON® is very similar to the natural human FSH, which is normally secreted by a small gland at the base of the brain, the pituitary. Together with luteinizing hormone (LH), FSH controls the action of the sexual glands (ovaries in women and testes in men).

In women FSH is important for the monthly ripening of the follicle, a tiny cyst in the ovary in which the egg cell develops. If the body does not produce enough FSH, infertility may be the result. In these cases PUREGON® can be used to make up for the shortage. To determine the right dosage, a daily check may be necessary. Follicle ripening is determined by means of ultrasound, and the amount of estrogens (female hormones) in blood can be measured. When the follicle is big enough, a hormone preparation with a strong LH activity is given (human chorionic gonadotropin, hCG). This causes ovulation (release of the egg).

In spite of careful monitoring, often more than one egg cell is released. This increases the chance of having more than one baby.

Poor production of FSH is not the only reason for infertility. In these cases medically assisted reproduction programs can sometimes be used, for instance *in vitro* ("test tube") fertilization. For this technique several egg cells are needed and PUREGON® can then be used to cause a number of egg cells to develop.

In men, it is used to increase the production of sperm in those who have a deficiency due to hypogonadotrophic hypogonadism.

When it should not be used:

Do not use PUREGON® if you are hypersensitive to follitropin beta or any of the other ingredients of PUREGON®, or if you have a tumour of the ovaries, breasts, uterus, testis, pituitary gland, or if you suffer from primary testicular failure.

Treatment with gonadotropins may increase the risk of having a blood clot (thrombosis). Thrombosis is the formation of a blood clot in your veins or arteries. Please tell your doctor prior to starting treatment, if you already know you have an increased risk for thrombosis, if you or anyone in your immediate family has ever had a thrombosis, or if you are severely overweight. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.

Blood clots can lead to serious medical conditions, such as:

- blockage in your lungs (pulmonary embolus)
- stroke
- heart attack
- blood vessel problems (thrombophlebitis)
- a lack of blood flow (deep venous thrombosis) that may result in a loss of your arm or leg.

Close supervision of patients by a doctor is very important. Usually ultrasound scans of the ovaries are performed. Your doctor may also check blood hormone levels. The results of these tests allow the doctor to choose the proper dose from day to day. This is very important since too high a dose may lead to rare but serious complications in which the ovaries are overly stimulated and the growing follicles become larger than normal. This serious medical condition is called ovarian hyperstimulation syndrome (OHSS). In rare cases, severe OHSS may be life-threatening. OHSS causes fluid to build up suddenly in your stomach and chest areas and can cause blood clots to form. Call your doctor right away if you notice severe abdominal swelling, pain in the stomach area (abdomen), feeling sick (nausea), vomiting, sudden weight gain due to fluid buildup, diarrhea, decreased

urine output or trouble breathing.

Ovarian Torsion: Ovarian torsion has occurred after treatment with gonadotropins including PUREGON®. Ovarian torsion is the twisting of an ovary. Twisting of the ovary could cause the blood flow to the ovary to be cut off.

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

Pregnancy: In pregnancies occurring after treatment with gonadotropic preparations, there is an increased risk of having twins or multiple births.

There is a slightly increased risk of a pregnancy outside of the uterus (an ectopic pregnancy). Early ultrasound confirmation that a pregnancy is intra-uterine is therefore important.

Ability to drive or operate machinery: As far as is known, PUREGON® has no effect on alertness and concentration.

What the medicinal ingredient is:
Follitropin beta

What the important nonmedicinal ingredients are:
In addition to FSH, both the solution in cartridges and the solution for injection contain L-methionine, polysorbate 20, sucrose, sodium citrate, and water for injection. Additionally, the solution in cartridges contains benzyl alcohol.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
PUREGON® only works if it is injected. It is presented as a sterile solution in cartridges in strength of 833 IU/mL. The 300 IU/0.36 mL cartridge contains 0. 480 mL for a net total deliverable dose of 300 IU, the 600 IU/0.72 mL cartridge contains 0.840 mL for a net total deliverable dose of 600 IU and the 900 IU/1.08 mL cartridge contains 1.23 mL for a net total deliverable dose of 900 IU.

The net total dose per 300, 600 or 900 IU cartridge is based on a maximum number of 6, 6 or 9 injections, respectively. When more injections are given the net total may be lowered, because each injection has to be preceded by an air shot. Air shots are used to remove excess air from the cartridge and the needle. (For example, for the 300 IUcartridge when administering a 50 IU dose, a maximum of 6 injections can be delivered for a net dose of 300 IU respectively. For the 600 & 900 IU cartridge, when administering a 100 IU dose, a maximum of 6 & 9 injections can be delivered for a net dose of 600 & 900 IU respectively).

PUREGON® is also presented as a sterile solution for injection. The 100 IU/0.5 mL vial containing the sterile solution has a red coloured tamper-evident disc, which is flipped off prior to insertion of the syringe needle.

WARNINGS AND PRECAUTIONS

BEFORE you use PUREGON® talk to your doctor or pharmacist:

- **Current conditions do not use this medication if you have;**
  - A high circulating FSH level indicating primary ovarian failure or primary testicular failure
  - Uncontrolled thyroid or adrenal dysfunction
  - Tumour of the ovary, breast, uterus, testis or brain (hypothalamus or pituitary gland)
  - Pregnancy, suspected pregnancy or lactation
  - Heavy or irregular vaginal bleeding of undetermined origin
  - Ovarian cyst or enlargement not due to polycystic syndrome (PCOS)
  - Are allergic (hypersensitive) to follitropin beta or any of the other ingredients of PUREGON®
  - Conditions incompatible with pregnancy such as malformations of reproductive organs or fibroid tumours of the uterus

- **Before starting to use this medicine, it is important to inform your doctor if you:**
  - Have experienced an allergic reaction to neomycin and/or streptomycin (antibiotics) in the past.
  - Have uncontrolled pituitary gland or hypothalamic problems.
  - Have an underactive thyroid gland (hypothyroidism).
  - Have adrenal glands that are not working properly (adrenocortical insufficiency).
  - Have high prolactin levels in the blood (hyperprolactinemia).
  - Have any other medical conditions (for example, diabetes, heart disease, or any other long-term disease).
  - If you are a woman:
  - Have ever had ovarian hyperstimulation syndrome OHSS.
  - Are pregnant or think that you may be pregnant.
  - Have ever had stomach (abdominal) surgery.

- Have ever had a twisting of an ovary.
- Have past or current cysts in your ovary or ovaries.

- **Past diseases**
  - Women with risk factors for thrombosis (previous episode of thrombosis, family history of thrombosis or a genetic condition that predisposes her to thrombosis) may have an increased risk of a venous or arterial thromboembolic event upon treatment with gonadotropins.

- **Reproductive issues**
  - After treatment with gonadotropin preparations, there is an increased chance of having multiple pregnancies, even when only one embryo is transferred into the uterus. 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, genetic background of both parents) may be associated with an increased risk of birth defects. There are also potential risks associated with multiple births including a higher rate of spontaneous abortion.
  - There is a slightly increased risk of a pregnancy outside of the uterus (an ectopic pregnancy). Therefore, your doctor should perform an early ultrasound examination to exclude the possibility of pregnancy outside the uterus.
  - There have been reports of ovarian and other reproductive system tumours in women who have had infertility treatment. It is not known if treatment with fertility medicines increases the risk of these tumours in infertile women.

- **Other medical conditions**
  - In addition, before starting to use this medicine, tell your doctor if you have been told by a doctor that pregnancy would be dangerous for you.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with PUREGON® include: clomiphene

PROPER USE OF THIS MEDICATION

PUREGON® solution for injection in cartridges has been developed for use in the 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.

Usual Dose:
Dosage in the female:
Your doctor will decide on the dose of PUREGON® to be given. This dose may be increased as your treatment progresses.
There are large differences between women in the response of the ovaries to FSH which makes it impossible to set a dosage schedule that 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.

Dosage in the male:
PUREGON® is usually prescribed at a dose of 450 IU per week, mostly given in 3 dosages of 150 IU per week **or** (also considered acceptable two dosages of 225 IU per week) both regimens given in combination with another hormone (hCG), for at least 3 to 4 months. Semen analysis is recommended 4 to 6 months after start of treatment to assess the response. If you have not responded after this period, your treatment may continue up to 48 weeks. Current clinical experience with other gonadotropins suggests that treatment for up to 18 months or longer may be necessary to achieve spermatogenesis.

How the injections are given: Using the pen, the injections are given slowly under the skin (for instance in the abdominal wall or in the upper thigh). The needle should be inserted at a 90° angle to the surface of the skin.

Using the solution for injection, flip - off the tamper - evident disc before insertion of the syringe needle. Tilt vial slightly before drawing up solution. The injections can be given under the skin or into a muscle. Your doctor will explain in more detail these two methods of injection.

To prevent painful injections and minimise leakage from the injection site, PUREGON® should be slowly administered intramuscularly or subcutaneously.

By whom: Using the solution in cartridges with the PUREGON PEN®, injections just under the skin can be given by you or your partner. Your doctor will tell you when and how to do this. The first injection of

PUREGON® should be given under medical supervision.

For women the PUREGON® solution for injection can be injected under the skin or into a muscle. Injections just under the skin can be given by you or your partner. The injections into a muscle should only be given by a doctor or nurse. For men the PUREGON® solution for injection can only be administered under the skin since injection into a muscle has not been investigated in this population. Your doctor will tell you when and how to inject. The first injection of PUREGON® should be given under medical supervision.

Overdose:
The acute toxicity of gonadotropins has been shown to be very low. Too high a dosage for more than one day may lead to hyperstimulation of the ovaries (OHSS).

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose contact your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following adverse reactions have been reported with gonadotropin therapy in general: mild to moderate ovarian enlargement; febrile reactions which may be associated with chills, musculoskeletal aches, joint pains, malaise, headache and fatigue; breast tenderness; dry skin; hair loss; hives; and hemoperitoneum.

The following reactions were observed during clinical trials; vaginitis, abdominal pain - upper/lower, nausea, abdominal discomfort, urinary tract infection, ovarian cyst, headache, vomiting, loose stools, faint feeling, laboured breathing, nasal congestion, sore throat, upper respiratory tract infection and nervousness.

The following adverse events have been reported subsequent to pregnancies resulting from gonadotropin therapy: tubal pregnancy; congenital abnormalities and birth defects. None of these events were considered drug-related and the incidence does not exceed that found in the general population. Spontaneous abortion was also observed in patients receiving urinary gonadotropin therapy. A slightly increased risk of multiple gestations has been seen.

The greatest concern your doctor will have is ovarian hyperstimulation syndrome (OHSS). To avoid the development of OHSS, your doctor will carefully monitor your response to PUREGON®. Ovarian enlargement, sometimes accompanied by abdominal bloating may occur in about 20% of women taking gonadotropins. This is generally reversed with cessation of treatment and severe life-threatening cases are rare.

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 the male: Common side effects (likely to affect 1 to 10 users in 100):
- Acne
- Hardening of the injection site
- Headache
- Rash
- Some breast development
- Testicular cyst

Clinical use of PUREGON® 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. Generalized hypersensitivity reactions including erythema, urticaria, rash and pruritus have been observed uncommonly (approximately 0.2% of all patients treated with PUREGON®).

Treatment of women

A complication with FSH treatment is unwanted overstimulation of the ovaries. Ovarian overstimulation may develop into a medical condition called **ovarian hyperstimulation syndrome (OHSS)**, which can be a serious medical problem. The risk can be reduced by careful monitoring of follicle development during treatment. Your doctor will do ultrasound scans of your ovaries to carefully monitor the number of maturing follicles. Your doctor may also check blood hormone levels. The first symptoms of ovarian overstimulation may be noticed as pain in the stomach (abdomen), feeling sick or diarrhea. In more severe cases symptoms may include enlargement of the ovaries, accumulation of fluid in the abdomen and/or chest (which may cause sudden weight gain due to fluid buildup) 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.

Common side effects (likely to affect 1 to 10 users in 100):
- Headache
- Injection site reactions (such as bruising, pain, redness, swelling and itching)
- Ovarian hyperstimulation syndrome (OHSS)
- Pelvic pain
- Stomach pain and/or bloating

Uncommon side effects (likely to affect 1 to 10 users in 1,000)
- Breast complaints (including tenderness)
- Diarrhea, constipation or stomach discomfort
- Enlargement of the uterus
- Feeling sick
- Hypersensitivity reactions (such as rash, redness, hives and itching)
- Ovarian cysts or enlargement of the ovaries
- Ovarian torsion (twisting of the ovaries)
- Vaginal bleeding

Rare side effects (likely to affect 1 to 10 users in 10,000)
- Blood clots (this may also occur in the absence of unwanted overstimulation of the ovaries).

Pregnancy outside the uterus (an ectopic pregnancy), miscarriage and multiple pregnancies have also been reported. These side effects are not considered to be related to the use of PUREGON®, but to Assisted Reproductive Technology (ART) or subsequent pregnancy.

This is not a complete list of side effects. For any unexpected effects while taking PUREGON®, contact your doctor or pharmacist immediately.

HOW TO STORE IT

Keep out of reach and sight of children. Do not use past expiry date. Protect from light.

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

Patient: Store in a refrigerator (2ºC - 8ºC) (do not freeze) **or** store at or below 25ºC for a maximum of 3 months (keep the cartridges or vials in the outer carton).

PUREGON® Solution for Injection in Cartridge:
Once the rubber inlay of a cartridge is pierced by a needle, the product may be stored for a maximum of 28 days.

PUREGON® Solution for Injection in Vials:
The contents of a vial should be used immediately after piercing of the rubber stopper.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

or at Merck Canada Inc. by one of the following 2 ways:

- Call toll-free at 1-800-567-2594
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-877-428-8675, or
  - Mail to: Merck Canada Inc.
    Medical Information Center
    16750 route Transcanadienne
    Kirkland, QC H9H 4M7

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program or Merck do not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.merck.ca or by contacting the sponsor, Merck Canada Inc. at: 1-800-567-2594.

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