PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**REKOVELLE®**

follitropin delta injection

Prefilled cartridges

12 µg/0.36mL, 36 µg/1.08mL and 72 µg/2.16mL

Subcutaneous Injection

Pharmaceutical Standard: Professed

Therapeutic classification: Gonadotropin

REKOVELLE (follitropin delta) should be prescribed and supervised by physicians who are experienced in the management of patients undergoing fertility treatment and who have fully familiarized themselves with the efficacy and safety profile of REKOVELLE.

Sponsor:
Ferring Inc.
200 Yorkland Blvd., Suite 500
Toronto, Ontario, M2J 5C1

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REKOVELLE

(follitropin delta injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Solution for injection/ 33.3 µg/mL in prefilled cartridges 12 µg/0.36 mL 36 µg/1.08 mL 72 µg/2.16 mL	Phenol, polysorbate 20, L-methionine, sodium sulfate decahydrate, disodium hydrogen phosphate dodecahydrate, phosphoric acid, sodium hydroxide and water for injections

DESCRIPTION

REKOVELLE (follitropin delta injection) is a recombinant human FSH produced in a human cell line by recombinant DNA technology. The amino acid sequences of the two FSH subunits in REKOVELLE are identical to the endogenous human FSH sequences. The expressing cell line can influence the characteristics of the recombinant FSH, and differences in glycosylation profile, sialic acid pattern and isoform profile have been documented between REKOVELLE and recombinant FSH products such as follitropin alfa and follitropin beta produced in Chinese hamster ovary (CHO) cell lines. Comparisons of REKOVELLE versus follitropin alfa indicate that the differences in glycosylation influence both the pharmacokinetic and pharmacodynamic profile.

INDICATIONS AND CLINICAL USE

REKOVELLE (follitropin delta injection) is indicated for controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle.

Selection of patients

Before treatment with REKOVELLE is instituted, a thorough gynaecologic and endocrinologic evaluation must be performed. This should include an assessment of pelvic anatomy.

Primary ovarian failure should be excluded by the determination of gonadotropin levels. Appropriate evaluation should be performed to exclude pregnancy.

Patients in late reproductive life have a greater predisposition to endometrial carcinoma. A thorough diagnostic evaluation should always be performed in patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities before starting REKOVELLE therapy.

Evaluation of the partner's fertility potential should be included in the initial evaluation.

The product should be used under the supervision of a qualified health professional who is experienced in the use of fertility treatments and in the management of ovarian hyperstimulation syndrome (OHSS), which is the most critical safety concern associated with the use of gonadotropin preparations. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

Geriatrics (> *65* years of age):
Not indicated for treatment in geriatric population.

Pediatrics (<18 years of age):
Not indicated for use in the pediatric population.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Tumours of the hypothalamus or pituitary gland
- Ovarian enlargement or ovarian cyst not due to polycystic ovarian syndrome
- Gynaecological haemorrhages of unknown aetiology
- Ovarian, uterine or mammary carcinoma
- Pregnancy and lactation

REKOVELLE must not be used when an effective response cannot be obtained, such as:

- Primary ovarian failure
- Malformations of sexual organs incompatible with pregnancy
- Fibroid tumours of the uterus incompatible with pregnancy

WARNINGS AND PRECAUTIONS

General

Careful attention should be given to diagnosis in candidates for REKOVELLE (follitropin delta injection) therapy (see INDICATIONS AND CLINICAL USE: Selection of Patients).

REKOVELLE contains a potent gonadotropic substance capable of causing mild to severe adverse reactions, and should only be used by physicians who are thoroughly familiar with infertility problems and their management.

Gonadotropin therapy requires time commitment by physicians and supportive healthcare professionals, as well as the availability of appropriate monitoring facilities (see Monitoring and Laboratory Tests). Safe and effective use of REKOVELLE requires monitoring of ovarian response with ultrasound alone, or in combination with measurement of serum estradiol levels, on a regular basis.

The dose of REKOVELLE is individualized for each patient to obtain an ovarian response with favorable safety/efficacy profile. There may be a degree of interpatient variability in response to FSH administration, with poor response to FSH in some patients and exaggerated response in others.

Use of results obtained with assays other than the Elecsys® AMH immunoassay from Roche for REKOVELLE dose determination is not recommended, as there currently is no standardization of available AMH assays.

Prior to therapy with REKOVELLE, patients should be informed of the duration of treatment and monitoring of their condition that will be required. Possible adverse reactions (see ADVERSE REACTIONS) should also be discussed.

Patients undergoing stimulation of follicular growth may experience ovarian enlargement and may be at risk of developing ovarian hyperstimulation syndrome (OHSS). Adherence to the REKOVELLE dose and regimen of administration and careful monitoring of therapy will minimize the incidence of such events.

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism and hyperprolactinemia, and the appropriate specific treatment should be given.

<u>Ovarian Hyperstimulation Syndrome (OHSS)</u>

A certain degree of ovarian enlargement is an expected effect of controlled ovarian stimulation. It is more commonly seen in patients with polycystic ovarian syndrome and usually regresses without treatment. In distinction to uncomplicated ovarian enlargement, OHSS is a condition that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.

It is important to stress the value of careful and frequent monitoring of follicular development in order to reduce the risk of OHSS *(see Monitoring and Laboratory Tests)*. The following symptoms may be observed in severe cases of OHSS: abdominal pain, discomfort and distension, severe ovarian enlargement, weight gain, dyspnea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhea. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, or acute pulmonary distress. Very rarely, severe OHSS may be complicated by ovarian torsion *(see Sexual Function and Reproduction)* or thromboembolic events such as pulmonary embolism, ischaemic stroke or myocardial infarction (*see Cardiovascular*).

Excessive ovarian response to gonadotropin treatment seldom gives rise to OHSS unless hCG is administered to trigger final follicular maturation. Furthermore, the syndrome may be more severe and more protracted if pregnancy occurs. Therefore, in cases of ovarian hyperstimulation (*see Monitoring and Laboratory Tests*) it is prudent to withhold hCG and advise the patient to refrain from coitus or to use barrier contraceptive methods for at least 4 days.

OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event. It most often occurs after hormonal treatment has been discontinued. Also, as a consequence of the hormonal changes during pregnancy, late development of OHSS can occur. Because of the risk of developing OHSS patients should be followed for at least two weeks after triggering of final follicular maturation.

Carcinogenesis and Mutagenesis
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.

No genotoxicity studies and carcinogenicity studies have been conducted, since FSH is an endogenous protein hormone.

Cardiovascular
Thromboembolic events
Women with recent or ongoing thromboembolic disease or women with generally recognised risk factors for thromboembolic events, such as personal or family history, severe obesity (body mass index >30 kg/m^2) or thrombophilia may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotropins. Treatment with gonadotropins may further increase the risk for aggravation or occurrence of such events. In these women, the benefits of gonadotropin administration need to be weighed against the risks. It should be noted however that pregnancy itself as well as OHSS also carry an increased risk of thromboembolic events.

Respiratory
Serious pulmonary conditions (e.g. atelectasis, acute respiratory distress syndrome and exacerbation of asthma) have been reported following gonadotropin therapy. No severe respiratory adverse reactions were observed in clinical studies with REKOVELLE.

Sexual Function/Reproduction

Ovarian torsion
Occurrence of ovarian torsion has been reported for ART cycles. It 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.

Multiple pregnancy
Multiple pregnancy carries an increased risk of adverse maternal and perinatal outcomes. In patients undergoing ART procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient age, although twin pregnancy can in rare occations develop from single embryo transfers. The patients should be advised of the potential risk of multiple births before starting treatment.

Pregnancy loss
The incidence of pregnancy loss by miscarriage or abortion is higher in patients undergoing controlled ovarian stimulation for ART than following natural conception.

Ectopic pregnancy
Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after ART has been reported to be higher than in the general population.

Congenital malformation
The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and multiple pregnancy.

Other medical conditions
Medical conditions that contraindicate pregnancy should also be evaluated before starting treatment with REKOVELLE.

Reproductive system neoplasms
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. It is not established whether or not treatment with gonadotropins increases the risk of these tumors in infertile women.

Special Populations

Pregnant Women
REKOVELLE is contraindicated during pregnancy.

Nursing Women
REKOVELLE is contraindicated during lactation.

Patients with renal and hepatic impairment
Safety, efficacy and pharmacokinetics of REKOVELLE in patients with renal or hepatic impairment have not been established.

Polycystic ovarian syndrome patients
Polycystic ovarian syndrome patients with anovulatory disorders have not been studied.

Monitoring and Laboratory Tests
Serum anti-Müllerian hormone (AMH) concentration, which is a biomarker of ovarian response to gonadotropins, should be measured prior to treatment, to determine the initial dose. The dose should be based on a recent determination of AMH (i.e. within the last 12 months) measured by the following diagnostic test from Roche: Elecsys® AMH immunoassay.

Follicular development during treatment with REKOVELLE should be assessed by monitoring with ultrasound alone or in combination with measurement of serum estradiol levels. Adequate follicular development is achieved on average by the ninth day of treatment (range 5 to 20 days).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequently reported adverse drug reactions (≥1%) with REKOVELLE in clinical phase III studies were headache, pelvic discomfort, ovarian hyperstimulation syndrome (OHSS), pelvic pain, nausea, adnexa uteri pain and fatigue.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The pivotal clinical phase III trial with REKOVELLE was ESTHER-1, conducted in women aged 18-40 years undergoing controlled ovarian stimulation for IVF/ICSI *(see Clinical Trials)*. The ESTHER-2 trial was conducted in women who did not achieve pregnancy in the ESTHER-1 trial, and the main objective was to assess the immunogenicity of REKOVELLE after up to two additional treatment cycles.

In ESTHER-1, women treated with REKOVELLE had their individual dose determined on the basis of their AMH level at screening and their body weight at randomisation. In ESTHER-2, the REKOVELLE dose was established based on the ovarian response in the previous stimulation cycle. Within each cycle, the daily REKOVELLE dose was fixed throughout the stimulation period.

Table 1 displays the adverse drug reactions in patients treated with REKOVELLE or GONAL-F in the phase III study ESTHER-1 according to system organ class and frequency.

Table 1 Adverse Drug Reactions (≥1%) in ESTHER-1 study

	REKOVELLE n = 665 (%)	**GONAL-F n = 661 (%)**
Any adverse drug reactions	17.0%	13.8%
Gastrointestinal disorders	3.2%	2.0%
Nausea	1.7%	1.1%
General disorders and administration site conditions	2.0%	0.9%
Fatigue	1.8%	0.9%
Nervous system disorders	5.6%	5.0%
Headache	5.3%	4.5%
Reproductive system and breast disorders	10.1%	9.8%
Pelvic discomfort	3.8%	3.2%
Ovarian hyperstimulation syndrome	3.0%	3.6%
Pelvic pain	2.0%	2.6%
Adnexa uteri pain	1.2%	0.6%

Table 2 displays the adverse drug reactions in patients treated with REKOVELLE or GONAL-F in the phase III study ESTHER-2 according to system organ class and frequency.

Table 2 Adverse Drug Reactions (≥1%) in ESTHER-2 study

	Cycle 2		Cycle 3	
	REKOVELLE n = 252 (%)	**GONAL-F n = 261 (%)**	**REKOVELLE n = 95 (%)**	**GONAL-F n = 93 (%)**
Any adverse drug reactions	10.3%	13.8%	6.3%	10.8%
Gastrointestinal disorders	1.6%	3.1%	0%	1.1%
Nausea	1.2%	2.3%	0%	0%
Constipation	0%	0%	0%	1.1%
General disorders and administration site conditions	0.4%	1.5%	0%	2.2%
Fatigue	0%	1.5%	0%	2.2%
Nervous system disorders	3.6%	5.0%	1.1%	4.3%
Headache	3.2%	3.8%	1.1%	2.2%
Dysgeusia	0%	0.8%	0%	2.2%
Reproductive system and breast disorders	6.3%	9.6%	5.3%	4.3%
Pelvic discomfort	2.0%	2.3%	0%	2.2%
Adnexa uteri pain	2.0%	1.9%	2.1%	1.1%
Ovarian hyperstimulation syndrome	0.8%	2.3%	1.1%	0%
Pelvic pain	1.6%	1.5%	0%	0%
Nipple pain	0%	0%	1.1%	0%
Uterine polyp	0%	0%	1.1%	0%
Ovarian cyst	0%	0.4%	0%	1.1%

Less Common Clinical Trial Adverse Reactions
Gastrointestinal disorders: Diarrhoea (0.6%), Vomiting (0.2%), Constipation (0.3%), Abdominal discomfort (0.2%)
Nervous system disorders: Somnolence (0.2%), Dizziness (0.4%)
Psychiatric disorders: Mood swings (0.4%)
Reproductive system and breast disorders: Vaginal hemorrhage (0.2%), Breast pain (0.2%), Breast tenderness (0.2%)

Post-Market Adverse Drug Reactions
Ovarian torsion has been reported in connection with OHSS.

Immunogenicity - Anti-FSH Antibodies
Anti-FSH antibodies were measured pre-dosing and post-dosing in patients undergoing up to three repeated treatment cycles with REKOVELLE. Before exposure to REKOVELLE, the incidence of anti-FSH antibodies was 1.4%, and after treatment with REKOVELLE it was 1.1% in cycle 1, 0.8% in cycle 2 and 1.1% in cycle 3. In all patients with anti-FSH antibodies, titres were undetectable or very low and without neutralizing capacity.

DRUG INTERACTIONS

Overview
No dedicated drug-drug interaction studies have been performed.

Since REKOVELLE is a protein, it is highly unlikely that REKOVELLE would bind to plasma proteins or interact with the CYP450 system, and therefore no interactions with other medicinal products are anticipated. Moreover, potential clinically relevant interactions of exogenous FSH with other drugs have not been observed in the clinical studies investigating REKOVELLE, nor described in the literature.

Drug-Lifestyle Interactions
REKOVELLE is expected to have no or negligible influence on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosing of REKOVELLE (follitropin delta injection) is individualized for each patient to obtain an ovarian response with favorable safety/efficacy profile. REKOVELLE is dosed in micrograms (µg) and not in international units (IU) of biological activity. The dosing regimen is specific for REKOVELLE and the microgram dose cannot be applied to other gonadotropins. |

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

REKOVELLE is intended for subcutaneous administration and is designed to be used in conjunction with the REKOVELLE injection pen.

Recommended Dose and Dosage Adjustment

For the first treatment cycle, the individual daily dose will be determined on the basis of the woman's serum anti-Müllerian hormone (AMH) concentration and body weight. The dose should be based on a recent determination of AMH (i.e. within the last 12 months) measured by the following diagnostic test from Roche: ELECSYS AMH Plus immunoassay (*see Monitoring and Laboratory Tests*).
For calculation of the REKOVELLE dose, the body weight is to be measured without shoes and coat, just prior to start of stimulation.
The individual daily dose is to be maintained throughout the stimulation period.

For the first treatment cycle, the daily dose is 12 micrograms for women with AMH <15 pmol/L, irrespective of body weight.
For women with AMH ≥15 pmol/L the daily dose decreases from 0.19 to 0.10 micrograms/kg by increasing AMH concentration (see Table 3). The dose is to be rounded off to the nearest 0.33 micrograms to match the dosing scale on the injection pen.
The maximum daily dose for the first treatment cycle is 12 micrograms.
The AMH concentration is to be expressed in pmol/L and is to be rounded off to the nearest integer. If the AMH concentration is in ng/mL, the concentration should be converted to pmol/L by multiplying with 7.14 (ng/mL x 7.14 = pmol/L) before use.

Table 3. Calculation of daily dose based on AMH concentration

AMH concentration (pmol/L)	Daily dose fixed throughout stimulation
<15	12 µg
15-16	0.19 µg/kg
17	0.18 µg/kg
18	0.17 µg/kg
19-20	0.16 µg/kg
21-22	0.15 µg/kg
23-24	0.14 µg/kg
25-27	0.13 µg/kg
28-32	0.12 µg/kg
33-39	0.11 µg/kg
≥40	0.10 µg/kg
Example of rounding-off AMH concentration: AMH: 16.6 pmol/L is rounded off to 17 pmol/L (nearest integer)	

Treatment with REKOVELLE should be initiated day 2 or 3 after start of menstrual bleeding, and continue until adequate follicular development has been achieved as assessed by monitoring with ultrasound alone or in combination with measurement of serum estradiol levels. Adequate follicular development is achieved on average by the ninth day of treatment (range 5 to 20 days). As soon as ≥3 follicles ≥17 mm are observed, a single injection of 250 micrograms recombinant human chorionic gonadotropin (hCG) or 5,000 IU hCG is administered to induce final follicular maturation. In patients with excessive ovarian response of >25 follicles with a diameter ≥12 mm, triggering of final follicular maturation should not be performed and the cycle cancelled.

For subsequent treatment cycles, the daily dose of REKOVELLE should be maintained or modified according to the patient's ovarian response in the previous cycle. If the patient had adequate ovarian response in the previous cycle without developing OHSS, the same daily dose of REKOVELLE should be used. In case of ovarian hypo-response in the previous cycle, the daily dose of REKOVELLE in the subsequent cycle may be increased by 25%, according to the extent of response observed. There is limited data regarding subsequent use of REKOVELLE in patients who demonstrated ovarian hyper-response or developed OHSS. The management of these patients should be based on physician discretion. The maximum daily dose is 24 micrograms.

Missed Dose
For patients who miss a dose, it is not recommended to double the next dose. The patients should be reminded to contact the physician monitoring their treatment.

Administration
REKOVELLE is designed for use in conjunction with the REKOVELLE injection pen and is intended for subcutaneous administration, preferably in the abdominal wall.

Treatment with REKOVELLE should be initiated under the supervision of a physician experienced in the treatment of fertility problems. Patients must be educated on how to use the REKOVELLE injection pen and to perform injections.

For instructions on the administration with the REKOVELLE injection pen, see "Instructions for Use"

OVERDOSAGE
The effect of an overdose is unknown, nevertheless, there is a risk that ovarian hyperstimulation syndrome (OHSS) may occur.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

REKOVELLE (follitropin delta injection) stimulates ovarian follicular growth in women who do not have primary ovarian failure. Follicle stimulating hormone (FSH, follitropin), the active component of REKOVELLE, is one of the key hormones regulating reproductive functions both in females and in males. In females, the ovary is the target organ, where binding of FSH to the FSH receptor triggers intracellular mechanisms that drive the hormonal and cellular events regulating the maturation of Graafian follicles and granulosa cell estrogen production.

REKOVELLE has the amino acid sequence identical to the endogenous human FSH for both α and β subunits but is distinct from other recombinant FSH products (such as follitropin alfa and follitropin beta) by sialic acid pattern, isoforms, and glycosylation profiles of the FSH protein.

Pharmacodynamics

In a Phase II dose-response study in patients undergoing controlled ovarian stimulation for IVF/ICSI, 265 women randomly received one of five dose levels of REKOVELLE (5.2 µg, 6.9 µg, 8.6 µg, 10.3 µg, or 12.1 µg) or GONAL-F (150 IU) with baseline serum Anti-Müllerian hormone (AMH) levels within 5.0 - 44.9 pmol/L. Following daily subcutaneous administration of REKOVELLE, at the end of stimulation, dose-related increase of follicles and the serum levels of estradiol, inhibin B and inhibin A was observed. The number of oocytes retrieved increases with the dose of REKOVELLE and serum AMH concentration. The average number of oocytes retrieved was 5.2, 7.9, 9.2, 10.5, 12.2, and 10.4 for 5.2 µg, 6.9 µg, 8.6 µg, 10.3 µg and 12.1 µg REKOVELLE and 150 IU GONAL-F groups, respectively.

Pharmacokinetics
The pharmacokinetic profile of REKOVELLE was investigated in healthy gonadotropin down-regulated female volunteers and in IVF/ICSI patients undergoing controlled ovarian stimulation.

Absorption:
After single subcutaneous administration of REKOVELLE, the median time to maximum serum concentration (t_{max}) was 20 hours. After a single daily subcutaneous administration of REKOVELLE for 7 days, the median t_{max} was 10 hours. The absolute bioavailability of REKOVELLE by the SC route was approximately 64%.

Distribution:
The volume of distribution (V_{ss}) in healthy women following intravenous administration was about 9 L. Following daily subcutaneous administrations of REKOVELLE at dose range of 5.2 – 12.1 µg, steady-state serum levels of FSH were reached within 6 to 7 days with accumulation to a three-fold higher concentration compared with the concentration after the first dose.

Metabolism:
The metabolism and excretion of REKOVELLE has not been studied.

Elimination:
In healthy women, following intravenous administration, the clearance of REKOVELLE was 0.3 L/h and the elimination half-life was 24 hours. Following single subcutaneous administration, the apparent clearance of REKOVELLE was 0.4 L/h and the elimination half-life was 40 hours. Following daily subcutaneous administration, the apparent clearance of REKOVELLE was 0.6 L/h and the elimination half-life was 28 hours.

In IVF/ICSI patients, following daily subcutaneous administration of REKOVELLE (dose range 5.2 µg -12.1 µg), the apparent clearance of FSH was 0.6 L/h, based on population PK analysis.

Special Populations and Conditions
No studies in special populations have been performed. The pharmacokinetics of REKOVELLE in patients with renal or hepatic insufficiency has not been established.

STORAGE AND STABILITY

Store refrigerated at 2 to 8°C, until expiry. Protect from exposure to light.
Do not freeze.

Within the shelf life, REKOVELLE may be removed from the refrigerator, and stored at or below 25°C for up to 3 months including the 28 day in-use period. After this period, do not refrigerate again and discard the product.

After first injection, store REKOVELLE at or below 25°C for up to 28 days. After this period, discard any unused material.

Keep in a safe place and out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

The REKOVELLE (follitropin delta injection) should not be administered if it contains particles or is not clear.

The REKOVELLE 12 µg, 36 µg and 72 µg cartridges are designed for use in conjunction with the REKOVELLE injection pen. The instructions for using the pen must be followed.

When cartridge is in use, keep it in the REKOVELLE injection pen.

Any unused solution must be discarded not later than 28 days after first injection.

Discard used needles immediately after injection in appropriate safety containers.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

REKOVELLE (follitropin delta injection) is a sterile solution for subcutaneous injection in a in 3 mL cartridge (Type I glass) with a plunger (halobutyl rubber) and an aluminium crimp cap with a rubber inlay.

REKOVELLE contains 33.3 µg/mL follitropin delta. The other ingredients are phenol, polysorbate 20, L-methionine, sodium sulfate decahydrate, disodium hydrogen phosphate dodecahydrate, phosphoric acid, sodium hydroxide and water for injections.

Cartridges are available in three strengths:
12.0 µg of follitropin delta in 0.36mL including 1 cartridge with 3 needles
36.0 µg of follitropin delta in 1.08mL including 1 cartridge with 6 needles
72.0 µg of follitropin delta in 2.16mL including 1 cartridge with 9 needles.
Cartridges are to be used with the REKOVELLE injection pen. The injection pen is intended for multiple uses.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: follitropin delta

Chemical name: recombinant human follicle-stimulating hormone (FSH)

Molecular formula:

The molecular formula for the α and β subunits are:

α subunit: $C_{437}H_{682}N_{122}O_{134}S_{13}$
β subunit: $C_{538}H_{833}N_{145}O_{171}S_{13}$

Molecular mass:

The average molecular weights of the glycosylated α and β subunits determined by MALDI-ToF-MS are approximately 15,200 and 18,500 Daltons, respectively. Thus, approximately 40 % of the total molecular weight of the molecule is due to glycosylation.

Structural Formula:

Follicle stimulating hormone is a heterodimer composed of one α and one β subunit. The amino acid sequence (black) and glycosylation sites (bold underline italic) of the mature α and β subunits are shown below:

FSH subunit α
1 APDVQDCPEC TLQENPFFSQ PGAPILQCMG CCFSRAYPTP LRSKKTMLVQ K***N***VTSESTCC
61 VAKSYNRVTV MGGFKVE***N***HT ACHCSTCYYH KS

FSH subunit β
1 NSCELT***N***ITI AIEKEECRFC ISI***N***TTWCAG YCYTRDLVYK DPARPKIQKT CTFKELVYET
61 VRVPGCAHHA DSLYTYPVAT QCHCGKCDSD STDCTVRGLG PSYCSFGEMK E

CLINICAL TRIALS

Study demographics and study design

The efficacy and safety of REKOVELLE was assessed in a randomised, controlled, assessor-blind, parallel groups, multicentre, multinational trial (ESTHER-1: Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World) in first cycle patients aged 18-40 years undergoing controlled ovarian stimulation for IVF/ICSI following a GnRH antagonist protocol. On day 2-3 of the menstrual cycle, 1329 women were randomised in a 1:1 ratio to treatment with either REKOVELLE or GONAL-F, and stimulation was initiated in 1326 women (665 with REKOVELLE and 661 with GONAL-F). Randomisation was stratified by centre and according to age (<35, 35-37 and 38-40 years).Women who were randomised to REKOVELLE had their individual dose determined on the basis of their AMH level at screening and their body weight at randomisation. The daily REKOVELLE dose was fixed throughout the stimulation period. For women with low AMH (<15 pmol/L) the daily REKOVELLE dose was 12 µg, irrespective of body weight. For women with high AMH (≥15 pmol/L) the daily REKOVELLE dose was dependent on AMH level and body weight and the maximum allowed daily dose of REKOVELLE was 12 µg. Women could be treated with REKOVELLE for a maximum of 20 days, and coasting was not allowed. For women randomised to GONAL-F the starting dose was 150 IU and fixed for the first five stimulation days after which it could be adjusted by 75 IU based on the individual response. The maximum daily GONAL-F dose allowed was 450 IU. Women could be treated with GONAL-F for a maximum of 20 days, and coasting was not allowed.

The summary of the ESTHER-1 clinical study in IVF/ICSI patients is shown in Table 4 below.

Table 4. Summary of the ESTHER-1 clinical study in IVF/ICSI patients

Study ID	Design	Treatments	Patients
ESTHER-1 (000004)	Randomised, controlled, assessor-blind, parallel groups, multicentre, multinational IVF/ICSI patients, 18-40 years	REKOVELLE: individualised dosing regimen based on AMH and body weight (max daily dose 12 µg SC); fixed dose throughout stimulation. AMH was analysed using the Elecsys® Plus AMH immunoassay from Roche Diagnostics GONAL-F: starting dose of 11 µg filled by mass (150 IU) SC; potential dose adjustments after the first 5 days	Total: 1,326 REKOVELLE: 665

AMH: anti-Müllerian hormone; ESTHER: Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilisation; IU: international units, SC: subcutaneous

The study enrolled-women who had been diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or had partners diagnosed with male factor infertility, and were considered eligible for IVF or ICSI.

One of the primary endpoints was ongoing pregnancy rate, defined as at least one intrauterine viable fetus 10-11 weeks after transfer.

There is no clinical trial experience with REKOVELLE in the long GnRH agonist protocol.

Study results

Efficacy

ESTHER-1 study

The study demonstrated that REKOVELLE was non-inferior to GONAL-F in terms of ongoing pregnancy rate, as shown in Table 5.

Table 5. Ongoing pregnancy rate in ESTHER-1 study in patients undergoing controlled ovarian stimulation for IVF/ICSI (mITT population)

	REKOVELLE in an individualized dosing regimen (N=665)	GONAL-F Follitropin alfa (N=661)	Difference between REKOVELLE and GONAL-F [95% CI]
Ongoing pregnancy rate	204 (30.7%)	209 (31.6%)	-0.9% [-5.9%; 4.1%]

Population: all randomized and exposed = modified intention-to-treat (mITT). Three patients randomized but not exposed were excluded from the mITT analysis.
The two-sided 95% confidence interval (CI) was established using the Mantel-Haenszel method to combine results across age strata. If the lower limit of the 95% CI of the estimated difference in ongoing pregnancy rate between REKOVELLE and GONAL-F was above the pre-planned margin of -8.0%, non-inferiority of REKOVELLE would be demonstrated.

The overall average number of oocytes retrieved among the women who underwent triggering of final follicular maturation was 9.6 for patients treated with REKOVELLE and 10.1 for patients treated with GONAL-F. The proportion of patients with 8-14 oocytes retrieved was 41.4% with REKOVELLE and 37.4% with GONAL-F.

NON-CLINICAL TOXICOLOGY

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and local tolerance. The overdose of follitropin delta resulted in exaggerated pharmacological actions. When administered in doses ≥0.8 micrograms/kg/day which is above the recommended maximal dose in humans, Follitropin delta had a negative effect on fertility and early embryonic development in rats.

PART III: PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

Pr REKOVELLE®
(follitropin delta injection)

Read this carefully before you start taking **REKOVELLE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **REKOVELLE**.

What is REKOVELLE used for?
REKOVELLE is used to treat female infertility and is used in women undergoing assisted reproduction programmes such as in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI).

How does REKOVELLE work?
REKOVELLE stimulates the ovaries to grow and develop many egg sacs / follicles, from which eggs are collected and fertilised in the laboratory (in vitro).

What are the ingredients in REKOVELLE?
Medicinal ingredients: follitropin delta
Non-medicinal ingredients: phenol, polysorbate 20, L-methionine, sodium sulphate decahydrate, disodium hydrogen phosphate dodecahydrate, phosphoric acid, sodium hydroxide, water for injection.

REKOVELLE contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium free".

REKOVELLE comes in the following dosage forms:
REKOVELLE is a clear colourless solution for injection. It is provided in a glass cartridge. Cartridges are available in the following strengths and packages:

- 12 µg/0.36 mL Pack of 1 cartridge and 3 needles
- 36 µg/1.08 mL Pack of 1 cartridge and 6 needles
- 72 µg/2.16 mL Pack of 1 cartridge and 9 needles

Do not use REKOVELLE if:

- You are allergic to follicle stimulating hormone or any of the other ingredients of this medicine
- You have a tumour of the uterus, ovaries, breasts, pituitary gland or hypothalamus
- You have enlarged ovaries or cysts on your ovaries (unless caused by polycystic ovarian disease)
- You suffer from bleeding from the vagina without any known cause

- You are pregnant or breastfeeding
- You have experienced an early menopause
- You have abnormal shape of the sexual organs which make a normal pregnancy impossible
- You have fibroids of the uterus which make a normal pregnancy impossible.

REKOVELLE should not be used in children and adolescent

No interaction studies have been performed with REKOVELLE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REKOVELLE. Talk about any health conditions or problems you may have, including if you:

Ovarian Hyperstimulation Syndrome (OHSS)
Gonadotropins like REKOVELLE may cause ovarian hyperstimulation syndrome (OHSS). This is when your follicles develop too much and become large cysts.
Talk to your doctor if you

- Experience abdominal pain, discomfort or swelling
- Experience nausea
- Are vomiting
- Experience diarrhoea
- Gain weight
- Have difficulty in breathing

The doctor may ask you to stop using this medicine.

Blood clotting problems (thromboembolic events)
Infertility treatment can increase the risk of this happening, especially if you are overweight or you or someone in your family (blood relative) have a known blood clotting disease (thrombophilia). Tell your doctor if you think this applies to you.

Twisting of an ovary (Ovarian torsion)
There have been reports of ovarian torsion (twisting of an ovary) following assisted reproductive technology treatment. Twisting of the ovary could cause the blood flow to the ovary to be cut off.

Multiple pregnancy and birth defects
When undergoing assisted reproductive technology treatment, the risk of having a multiple pregnancy (such as twins) is mainly related to the number embryos placed inside your womb, the quality of the embryos, and your age. Multiple pregnancy may lead to medical complications for you and your babies. Furthermore, the risk of birth defects may be slightly higher following infertility treatment, which is thought to be due to characteristics of the parents (such as your age, and your partner's sperm characteristics if applicable) and multiple pregnancy.

Pregnancy loss
When undergoing assisted reproductive technology treatment, you are more likely to have a miscarriage than if you conceive naturally.

Ectopic pregnancy
When undergoing assisted reproductive technology treatment, you are more likely to have a pregnancy outside the uterus (ectopic pregnancy) than if you conceive naturally. If you have a history of tubal disease, you have an increased risk of ectopic pregnancy.

Ovarian and other reproductive system tumours
There have been reports of ovarian and other reproductive system tumours in women who had undergone infertility treatment. It is not known if treatment with fertility medicines increase 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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take REKOVELLE:
REKOVELLE is developed for use in the REKOVELLE injection pen. The separate instructions for using the injection pen must be followed carefully. Do not use the cartridge if the solution contains particles or if the solution is not clear.

REKOVELLE is intended to be given by injection just under the skin (subcutaneously) and the normal administration site is the abdominal wall. The cartridge can be used for several injections.

The first injection of this medicine should be given under the supervision of a doctor or a nurse. Hereafter your doctor will decide if you can administer REKOVELLE by self-administration at home, but only after receiving adequate training.

If you have any further questions on the use of this medicine, ask your doctor.

Usual dose:
The REKOVELLE dose applicable to your first treatment cycle will be calculated by your doctor using the level of anti-Müllerian hormone (AMH) - a marker of how your ovaries will respond to stimulation with gonadotropins – in your blood and your body weight. Therefore the AMH result from a blood sample (taken within the last 12 months) should be available before you start treatment. Your body weight will also be measured before you start treatment. The REKOVELLE dose is stated in micrograms.

The daily REKOVELLE dose is fixed throughout the treatment period. Treatment is stopped when an appropriate number of egg sacs are present.

Your doctor will monitor the effect of REKOVELLE treatment. Depending on your response to the treatment, your doctor may decide to stop treatment with REKOVELLE and not give you the hCG injection.

If you use more REKOVELLE than you should
The effects of taking too much REKOVELLE are unknown. Nevertheless one could expect ovarian hyperstimulation syndrome (OHSS) to occur.

Overdose:
The effects of taking too much REKOVELLE are unknown. Nevertheless one could expect ovarian hyperstimulation syndrome (OHSS) to occur.

If you think you have taken too much REKOVELLE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to use REKOVELLE. Do not take a double dose to make up for a forgotten dose. Please contact your doctor as soon as you notice that you forgot a dose.

What are possible side effects from using REKOVELLE?
These are not all the possible side effects you may feel when taking REKOVELLE. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects:
Hormones used in treatment of infertility such as REKOVELLE may cause a high level of activity in the ovaries (ovarian hyperstimulation syndrome, OHSS). Symptoms may include pain, discomfort or swelling of the abdomen, nausea, vomiting, diarrhoea, weight gain or difficulty breathing. If you experience any of these symptoms you should contact a doctor immediately.

The risk of having a side effect is described by the following categories:

Common (may affect up to 1 in 10 people):
- Headache
- Nausea
- Ovarian hyperstimulation syndrome (OHSS)
- Pelvic pain and discomfort
- Ovarian or tubal pain
- Tiredness (fatigue)

Uncommon (may affect up to 1 in 100 people):

- Mood swings
- Sleepiness / drowsiness
- Dizziness
- Diarrhoea
- Vomiting
- Constipation
- Discomfort of the abdomen
- Vaginal bleeding
- Breast complaints (include breast pain, breast tenderness)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Ovarian hyperstimulation syndrome (OHSS)		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Do not use this medicine after the expiry date which is stated on the cartridge label or carton. The expiry date refers to the last day of that month.

Storage:
Store refrigerated (2°C – 8°C). Do not freeze.
Before use store in the original package in order to protect from light.
When cartridge is in use, keep it in the REKOVELLE injection pen.
Within the shelf life, REKOVELLE may be removed from the refrigerator, and stored at or below 25°C for up to 3 months including the 28 day in-use period. After this period, do not refrigerate again and discard the product.
After first injection, store REKOVELLE at or below 25°C for up to 28 days. After this period, discard any unused material.
Keep in a safe place and out of reach and sight of children.

If you want more information about REKOVELLE:
● Talk to your healthcare professional
● Find the most recent version of the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; (www.canada.ca/en/health-canada), the manufacturer's website www.ferring.ca, or by calling 1-866-384-1314.

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