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| Size | | |
| Submission | ☐NDA ☐Renewal ☒ Variation change detail no.: #186630 #275278 | |
| Code of previous version | REKOPFP12,36,72-I-MY-02.03 | |
| Changes | Rekovelle Tech Transfer (Filling) to New Facility at Vetter (RVS6) – addition of new manufacturing site<br>Dose Comparability (15mcg follitrophin delta is comparable to 225IU follitropin alfa) | |
| Reference | CCDS version 5 (R Company_Core_Data_Sheet-30994_5.0)<br>☐Core PIL version: | ☐SPC country/version/date:<br>☐LAC no.: |
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# REKOVELLE®

**12 micrograms/0.36 mL solution for injection in pre-filled pen**
**36 micrograms/1.08 mL solution for injection in pre-filled pen**
**72 micrograms/2.16 mL solution for injection in pre-filled pen**

## QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled multidose pen delivers 12 micrograms follitropin delta* in 0.36 mL solution.
One pre-filled multidose pen delivers 36 micrograms follitropin delta* in 1.08 mL solution.
One pre-filled multidose pen delivers 72 micrograms follitropin delta* in 2.16 mL solution.

One mL of solution contains 33.3 micrograms of follitropin delta*.
*recombinant human follicle-stimulating hormone (FSH) produced in a human cell line (PER.C6) by recombinant DNA technology.

Excipients: Phenol, polysorbate 20, L-methionine, sodium sulphate decahydrate, disodium phosphate dodecahydrate, phosphoric acid concentrated (for pH adjustment), sodium hydroxide (for pH adjustment), water for injections.

## PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen (injection).
Clear and colourless solution with a pH of 6.0-7.0.

## THERAPEUTIC INDICATIONS

Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle.

## DOSAGE AND METHOD OF ADMINISTRATION

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

The posology of REKOVELLE is individualized for each patient and aims to obtain an ovarian response which is associated with a favourable safety/efficacy profile, i.e. aims to achieve an adequate number of oocytes retrieved and reduce the interventions to prevent ovarian hyperstimulation syndrome (OHSS). REKOVELLE is dosed in micrograms (see section Pharmacodynamic properties). The dosing regimen is specific for REKOVELLE and the microgram dose cannot be applied to other gonadotropins.

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 her body weight. The dose should be based on a recent determination of AMH (i.e. within the last 12 months) measured

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by the following diagnostic tests: ELECSYS AMH Plus immunoassay from Roche (i.e. assay used in clinical development trials), or alternatively the ACCESS AMH Advanced from Beckman Coulter (see section Special warnings and precautions for use). The individual daily dose is to be maintained throughout the stimulation period. For women with AMH <15 pmol/L the daily dose is 12 micrograms, 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 (Table 1). 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.

For calculation of the REKOVELLE dose, the body weight is to be measured without shoes and overcoat just prior to start of stimulation.

**Table 1 Dosing regimen for first treatment cycle with REKOVELLE**

| **AMH (pmol/L)** | <15 | 15-16 | 17 | 18 | 19-20 | 21-22 | 23-24 | 25-27 | 28-32 | 33-39 | ≥40 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Fixed daily dose of REKOVELLE** | 12 mcg | 0.19 | 0.18 | 0.17 | 0.16 | 0.15 | 0.14 | 0.13 | 0.12 | 0.11 | 0.10 |
| | | mcg/kg | | | | | | | | | |

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.

mcg: micrograms

Time of initiating treatment with REKOVELLE depends on the type of protocol.

- in a protocol using a gonadotropin-releasing hormone (GnRH) antagonist, the treatment with REKOVELLE should be initiated on day 2 or 3 after start of menstrual bleeding;
- in a protocol using down-regulation with a GnRH agonist, the treatment with REKOVELLE should be initiated approximately 2 weeks after the start of agonist treatment.

Treatment should continue until adequate follicular development (≥3 follicles ≥17 mm) has been achieved, which on average is by the ninth or tenth day of treatment (range 5 to 20 days). 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 follicular development (of ≥25 follicles ≥12 mm), treatment with REKOVELLE should be stopped and triggering of final follicular maturation with hCG should not be performed.

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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 should be used. In case of ovarian hypo-response in the previous cycle, the daily dose in the subsequent cycle should be increased by 25% or 50%, according to the extent of response observed. In case of ovarian hyper-response in the previous cycle, the daily dose in the subsequent cycle should be decreased by 20% or 33%, according to the extent of response observed. In patients who developed OHSS or were at risk of OHSS in a previous cycle, the daily dose for the subsequent cycle should be 33% lower than the dose used in the cycle where OHSS or risk of OHSS occurred. The maximum daily dose is 24 micrograms.

In these patients, administration of a GnRH agonist instead of hCG or cycle cancellation could be considered for triggering of final follicular maturation. Administration of GnRH agonist can reduce, but not eliminate, the risk for OHSS and is applicable only for GnRH antagonist cycles. In case of GnRH agonist administration, embryos should not be replaced in the fresh cycle but cryopreserved for later use. In patients with excessive ovarian response of >35 follicles with a diameter ≥12 mm, triggering of final follicular maturation should not be performed and the cycle cancelled.

Patients with AMH > 35 pmol/L

Potential high responders (patients with AMH > 35 pmol/L) have not been studied in a protocol using down-regulation with GnRH agonist.

Patients with renal and hepatic impairment

Safety, efficacy and pharmacokinetics of REKOVELLE in patients with renal or hepatic impairment have not been specifically studied in clinical trials. Although limited, data did not indicate a need for a different dosing regimen of REKOVELLE in this patient population (see section Special warnings and precautions for use).

Patients with polycystic ovaries

Anovulatory patients with polycystic ovarian syndrome have not been studied.

Ovulatory patients with polycystic ovaries have been included in clinical trials (see section Pharmacodynamics properties).

Elderly

There is no relevant use of REKOVELLE in the elderly population.

Paediatric population

There is no relevant use of REKOVELLE in the paediatric population.

**Method of administration**

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REKOVELLE is intended for subcutaneous use, preferably in the abdominal wall. The first injection should be performed under direct medical supervision. Patients must be educated on how to use the REKOVELLE injection pen and to perform injections. Self-administration should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

For instructions on the administration with the pre-filled pen, see the “Instructions for Use”.

**CONTRAINDICATIONS**

- Hypersensitivity to the active substance or to any of the excipients listed in section 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

In the following situations, treatment outcome is unlikely to be favourable, and therefore REKOVELLE should not be administered:

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

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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. Safe and effective use of REKOVELLE calls for 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 favourable 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.

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.

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Use of results obtained with assays other than the ELECSYS AMH Plus immunoassay from Roche and the ACCESS AMH Advanced from Beckman Coulter for REKOVELLE dose determination is not recommended, as there currently is no standardization of available AMH assays.

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

**Ovarian Hyperstimulation Syndrome (OHSS)**

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. The following symptoms may be observed in severe cases of OHSS: abdominal pain, discomfort and distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, or acute pulmonary distress. Very rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events such as pulmonary embolism, ischaemic stroke or myocardial infarction.

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 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.

Other measures to be considered to reduce the risk of OHSS include administration of GnRH agonist instead of hCG for triggering of final follicular maturation. Administration of GnRH agonist can reduce, but not eliminate, the risk for OHSS and is applicable only for GnRH antagonist cycles.

OHSS may progress rapidly (within 24 hours) to several days to become a serious medical event. Early OHSS can occur within 9 days after triggering of final follicular maturation. Late OHSS can develop as a consequence of the hormonal changes during pregnancy 10 or more days after triggering of final follicular maturation. Because of the risk of developing OHSS patients should be followed for at least two weeks after hCG administration.

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**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/m2) 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.

**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 occasions 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.

**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 treatment. It is not established whether or not treatment with gonadotropins increases the risk of these tumours in infertile women.

**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.

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

**Sodium content**
REKOVELLE contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free".

## INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed with REKOVELLE. With pituitary desensitisation caused by a GnRH agonist, a longer duration of stimulation and therefore a higher total dose of REKOVELLE may be necessary to achieve adequate follicular response. Clinically significant interactions with other medicinal products have neither been reported during REKOVELLE therapy, nor are expected.

## FERTILITY, PREGNANCY AND LACTATION

**Pregnancy**
REKOVELLE is not indicated during pregnancy. No teratogenic risk has been reported, following controlled ovarian stimulation, in clinical use with gonadotropins. There are no data from the inadvertent exposure to REKOVELLE in pregnant women. Studies in animals have shown reproductive toxicity with REKOVELLE doses above the recommended maximal dose in humans (section Pre-clinical Safety Data).

**Lactation**
REKOVELLE is not indicated during breastfeeding.

**Fertility**
REKOVELLE is indicated for use in infertility (see section Therapeutic indications).

**Women of childbearing potential/contraception in males and females**
Not applicable.

## EFFECTS ON ABILITY TO DRIVE OR USE MACHINES

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

## UNDESIRABLE EFFECTS

**Summary of safety profile**
The most frequently reported adverse drug reactions (ADR) during treatment with REKOVELLE are ovarian hyperstimulation syndrome (OHSS), headache, pelvic pain, nausea and fatigue. OHSS occurred in approximately 6% of all patients and severe OHSS was reported in less than 0.9%. The frequency of these adverse reactions might decrease with repeated treatment cycles, as this has been observed in clinical trials.

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**Tabulated summary of adverse reactions**The table below (Table 2) displays the adverse drug reactions experienced in clinical trials by patients treated with REKOVELLE using the algorithm-based dosing regimen. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 2 Adverse drug reactions in pivotal clinical trials**

| System Organ Class | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) |
|---|---|---|
| Psychiatric disorders | | Mood swings |
| Nervous system disorders | Headache | Somnolence<br>Dizziness |
| Gastrointestinal disorders | Nausea | Diarrhoea<br>Vomiting<br>Constipation<br>Abdominal discomfort [a] |
| Reproductive system and breast disorders | OHSS [b]<br>Pelvic pain [c] | Vaginal haemorrhage<br>Breast discomfort [d] |
| General disorders and administration site conditions | Fatigue | |

a Abdominal discomfort includes abdominal pain/distention.

b OHSS is an intrinsic risk of the ovarian stimulation. Known gastrointestinal symptoms associated with OHSS include abdominal pain, discomfort, and distension, nausea, vomiting and diarrhoea. Ovarian torsion and thromboembolic events are known to be rare complications of ovarian stimulation treatment.

c Pelvic pain includes pelvic discomfort and adnexa uteri pain.

d Breast discomfort include breast pain, breast swelling, breast tenderness, and/or nipple pain.

**ADRs from post-marketing sources**

Post-marketing data is in line with adverse drug reactions reported in clinical trials presented in Table 2.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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**Overdose**

The effect of an overdose is unknown, nevertheless, there is a risk that OHSS may occur.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital systems, gonadotropins, ATC code: G03GA10

### Mechanism of action

The most important effect resulting from parenteral administration of FSH is the development of multiple mature follicles.

Follitropin delta is a recombinant human FSH. The amino acid sequences of the two FSH subunits in follitropin delta 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 follitropin delta produced in a human cell line and recombinant FSH products such as follitropin alfa and follitropin beta produced in Chinese hamster ovary (CHO) cell lines. The glycosylation of FSH in follitropin delta contains both α2,3 and α2,6-linked sialic acid (2,6-linked sialic acid is absent in CHO-derived recombinant FSH), different sugars such as N-acetylgalactosamine, additional linkages between carbohydrates such as bisecting N-acetylglucosamine, and a higher proportion of tetra-antennary structures and higher overall sialic acid content than CHO-derived recombinant FSH.

### Pharmacodynamic effects

Comparisons of REKOVELLE versus follitropin alfa indicate that the differences in glycosylation influence both the pharmacokinetic and pharmacodynamic profile. Following daily administration of equal IU doses of REKOVELLE and follitropin alfa as determined in the rat in vivo bioassay (Steelman-Pohley assay), higher ovarian response (i.e. estradiol, inhibin B and follicular volume and number) was observed in healthy women after administration of REKOVELLE compared to follitropin alfa.

As the Steelman-Pohley bioassay might not fully reflect the potency of the FSH in REKOVELLE in humans, REKOVELLE is dosed in micrograms and not in IU. The clinical data below shows that a comparable ovarian response can be obtained for:

- 10 micrograms follitropin delta and 150 IU follitropin alfa
- 15 micrograms follitropin delta and 225 IU follitropin alfa

The clinical trial data suggest that a daily dose of 10.0 [95% CI 9.2; 10.8] micrograms REKOVELLE provides an ovarian response close to that obtained with 150 IU/day follitropin

alfa. In a phase 3 trial (ADAPT-1), comparing an initial daily dose of 15 micrograms REKOVELLE to an initial daily dose of 225 IU follitropin alfa in a GnRH antagonist protocol using a conventional dosing regimen, a comparable ovarian response was observed with regards to number of oocytes retrieved, follicular development, and hormone levels.

The number of oocytes retrieved increases with the dose of REKOVELLE and serum AMH concentration. Conversely, increasing body weight leads to a decrease in the number of oocytes retrieved (only clinically relevant for REKOVELLE doses below 12 micrograms). Consequently, the REKOVELLE dosing regimen is based on serum AMH concentration and furthermore on body weight for doses lower than 12 micrograms (see section Dosage and method of administration).

**Clinical efficacy and safety**

The ESTHER-1 trial was a randomized, assessor-blinded, controlled trial in 1,326 IVF/ICSI patients. The trial compared the individualized dosing regimen of REKOVELLE where the daily dose is established for each patient and fixed throughout stimulation with no adjustments (see section Dosage and method of administration) to follitropin alfa filled-by-mass at a starting dose of 11 micrograms (150 IU) for the first five days followed by dose adjustments from day 6 of stimulation based on follicular development in a GnRH antagonist protocol. The patients were up to 40 years of age and had regular menstrual cycles presumed to be ovulatory. Single blastocyst transfer on day 5 was compulsory with the exception of patients 38-40 years in whom double blastocyst transfer was performed if no good-quality blastocysts were available. The two co-primary endpoints were ongoing pregnancy rate and ongoing implantation rate in the fresh cycle, defined as at least one intrauterine viable fetus 10-11 weeks after transfer and number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of blastocysts transferred, respectively.

The trial demonstrated that REKOVELLE was at least as effective as follitropin alfa in terms of ongoing pregnancy rate and ongoing implantation rate, as shown in Table 3.

**Table 3 Ongoing pregnancy rate and ongoing implantation rate in ESTHER-1 trial**

| | REKOVELLE in an individualized dosing regimen (N=665) | Follitropin alfa (N=661) | Difference [95% CI] |
|---|---|---|---|
| Ongoing pregnancy rate | 30.7% | 31.6% | -0.9% [-5.9%; 4.1%] |
| Ongoing implantation rate | 35.2% | 35.8% | -0.6% [-6.1%; 4.8%] |

Population: all randomized and exposed

The impact of the AMH-based dosing regimen of REKOVELLE was also assessed in secondary endpoints, such as ovarian response and OHSS risk management.

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In the overall trial population, the mean number of oocytes retrieved was 10.0 ± 5.6 with REKOVELLE (N=636) in the individualised dosing regimen and 10.4 ± 6.5 with follitropin alfa (N=643) at a starting dose of 150 IU followed by dose adjustments.

Among patients with AMH ≥15 pmol/L, the ovarian response with REKOVELLE (N=355) and follitropin alfa (N=353), respectively, was as follows: mean number of oocytes retrieved 11.6 ± 5.9 and 13.3 ± 6.9, and proportion of patients with ≥20 oocytes 10.1% (36/355) and 15.6% (55/353).

In ovulatory patients with polycystic ovaries undergoing a GnRH antagonist cycle, the incidence of early moderate/severe OHSS and/or preventive interventions for early OHSS was 7.7% with REKOVELLE and 26.7% with follitropin alfa.

In a controlled trial evaluating the ovarian response with individualised REKOVELLE dosing in patients with AMH ≤35 pmol/L, the mean number of oocytes was 11.1 ± 5.9 in a GnRH agonist cycle (N=202) compared to 9.6 ± 5.5 in a GnRH antagonist cycle (N=204), and the mean duration of stimulation with REKOVELLE was 10.4 ± 1.9 days in a GnRH agonist cycle compared to 8.8 ± 1.8 days in a GnRH antagonist cycle.

Safety – immunogenicity

Anti-FSH antibodies were measured pre-dosing and post-dosing in patients undergoing up to three repeated treatment cycles with REKOVELLE (665 patients in cycle 1 in the ESTHER-1 trial as well as 252 patients in cycle 2 and 95 patients in cycle 3 in the ESTHER-2 trial). The incidence of anti-FSH antibodies after treatment with REKOVELLE was 1.1% in cycle 1, 0.8% in cycle 2 and 1.1% in cycle 3. These rates were similar to the incidence of pre-existing anti-FSH antibodies before exposure to REKOVELLE in cycle 1 which was 1.4%, and comparable to the incidences of anti-FSH antibodies after treatment with follitropin alfa. In all patients with anti-FSH antibodies, titres were undetectable or very low and without neutralising capacity. Repeated treatment with REKOVELLE of patients with pre-existing or treatment-induced anti-FSH antibodies did not increase the antibody titre, was not associated with decreased ovarian response, and did not induce immune-related adverse events.

Clinical trial experience with REKOVELLE in the long GnRH agonist protocol is limited.

**Pharmacokinetic Properties**

The pharmacokinetic profile of follitropin delta has been investigated in healthy female subjects and in IVF/ICSI patients undergoing COS. Following repeated daily subcutaneous administrations, REKOVELLE reaches steady-state within 6 to 7 days with a threefold higher concentration compared with the concentration after the first dose. Circulating levels of follitropin delta are inversely related to the body weight, which supports individualized dosing based on body weight. Follitropin delta leads to greater exposure than follitropin alfa.

| Proposed packaging material | | |
|---|---|---|
| Code | REKOPFP12,36,72-I-MY-03.01 (RVS6) | |
| Size | | |
| Submission | ☐NDA ☐Renewal ☒ Variation change detail no.: #186630 #275278 | |
| Code of previous version | REKOPFP12,36,72-I-MY-02.03 | |
| Changes | Rekovelle Tech Transfer (Filling) to New Facility at Vetter (RVS6) – addition of new manufacturing site<br>Dose Comparability (15mcg follitrophin delta is comparable to 225IU follitropin alfa) | |
| Reference | CCDS version 5 (R Company_Core_Data_Sheet-30994_5.0)<br>☐Core PIL version: | ☐SPC country/version/date:<br>☐LAC no.: |
| Name & Date | BRKH 16-Jan-2026 | |

**Absorption**

After daily subcutaneous administration of REKOVELLE, the time to maximum serum concentration is 10 hours. The absolute bioavailability is about 64%.

**Distribution**

The volume of distribution at steady state is about 9 L. Within the therapeutic dose range, exposure to follitropin delta increases proportionally with the dose.

**Elimination**

Following intravenous administration, the clearance of follitropin delta is 0.3 L/h. The terminal elimination half-life after single subcutaneous administration is 40 hours and after multiple subcutaneous administration is 28 hours. Comparison of the pharmacokinetics of follitropin delta with follitropin alfa following daily subcutaneous administration of equal doses of IUs for 7 days, revealed that the AUC and Cmax are 1.7-fold and 1.6-fold higher for follitropin delta than for follitropin alfa. Follitropin delta is expected to be eliminated similarly to other follitropins, i.e. mainly by the kidneys. The fraction of follitropin delta excreted unchanged in the urine was estimated to 9%.

**PRECLINICAL SAFETY DATA**

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 pharmacological or exaggerated pharmacological actions. Follitropin delta had a negative effect on fertility and early embryonic development in rats when administered in doses ≥0.8 micrograms/kg/day which is above the recommended maximal dose in humans. The relevance of these findings for the clinical use of REKOVELLE is limited.

**INCOMPATIBILITIES**

Not applicable.

**SHELF LIFE**

3 years.

In use: 28 days when stored at or below 30 °C.

**SPECIAL PRECAUTION FOR STORAGE**

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Before first use, store in the original package in order to protect from light. During in use period, keep the pen cap on in order to protect from light.

**NATURE AND CONTENTS OF CONTAINER**

**REKOVELLE 12 micrograms/0.36 mL solution for injection in pre-filled pen**

| Proposed packaging material | | |
|---|---|---|
| Code | REKOPFP12,36,72-I-MY-03.01 (RVS6) | |
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| Submission | ☐NDA ☐Renewal ☒ Variation change detail no.: #186630 #275278 | |
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| Name & Date | BRKH 16-Jan-2026 | |

3 mL multidose cartridge (Type I glass) with a plunger (halobutyl rubber) and a crimp cap (aluminium) with an inlay (rubber). Each cartridge contains 0.36 mL of solution.
Pack size of 1 pre-filled pen and 3 injection needles (stainless steel).

**REKOVELLE 36 micrograms/1.08 mL solution for injection in pre-filled pen**
3 mL multidose cartridge (Type I glass) with a plunger (halobutyl rubber) and a crimp cap (aluminium) with an inlay (rubber). Each cartridge contains 1.08 mL of solution.
Pack size of 1 pre-filled pen and 6 injection needles (stainless steel).

**REKOVELLE 72 micrograms/2.16 mL solution for injection in pre-filled pen**
3 mL multidose cartridge (Type I glass) with a plunger (halobutyl rubber) and a crimp cap (aluminium) with an inlay (rubber). Each cartridge contains 2.16 mL of solution.
Pack size of 1 pre-filled pen and 9 injection needles (stainless steel).

## SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

The solution should not be administered if it contains particles or is not clear.
The instructions for use of the pen must be followed. Discard used needles immediately after injection.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## MANUFACTURED BY

Vetter Pharma-Fertigung GmbH & Co. KG
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Germany

## RELEASED BY

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Date of revision: Jan 2026