1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of the solution contains 33.3 micrograms of follitropin delta*.

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.

*recombinant human follicle-stimulating hormone (FSH) produced in a human cell line (PER.C6) by recombinant DNA technology.

No animal-derived materials are used in the REKOVELLE manufacturing processes.

Excipient(s) with known effect:
This medicinal product contains less than 1 mmol (23 mg) sodium per injection, i.e., essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen (injection).

Clear and colourless solution with a pH of 6.0-7.0.

4 CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration

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.

Posology

The posology of REKOVELLE is individualised for each patient to obtain an ovarian response 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) (see Section 5.1).

REKOVELLE is dosed in micrograms (μg) and not in international units (IU) of biological activity (see section 5.1). 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, which is a biomarker of ovarian response to gonadotropins,

and her 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 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 4.4). 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.

The AMH concentration is to be expressed in pmol/L and is to be rounded off to the nearest integer (Table 1). 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.

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

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

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

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). 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. 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.

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 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 of REKOVELLE 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 of REKOVELLE 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.

Elderly (more than 65 years)
There is no relevant use of REKOVELLE in the elderly population. Safety and efficacy of REKOVELLE in elderly patients have not been established.

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 with anovulatory disorders
Anovulatory patients with polycystic ovarian syndrome have not been studied. Ovulatory patients with polycystic ovaries have been included in clinical trials.

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

Method of administration
REKOVELLE is intended for subcutaneous administration, preferably in the abdominal wall. The first injection of REKOVELLE should be performed under direct medical supervision. Self-administration of REKOVELLE 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".

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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

4.4 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 individualised 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.

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 standardisation of available AMH assays.

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

<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. 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.

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.

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.

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".

Polysorbate content
REKOVELLE contains 0.005 mg of polysorbate 20 per ml.
Polysorbate may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed with REKOVELLE.

4.6 Pregnancy and lactation
REKOVELLE is contraindicated during pregnancy and breast-feeding (see Section 4.3).
Use in 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. Animal embryofetal development studies have not been performed with follitropin delta. Embryofetal toxicity (as dystocia and marked post-implantation loss, but not teratogenicity, has been observed with the closely related agent, follitropin alfa, in rats and rabbits as a result of exaggerated pharmacology.

Use in lactation
It is not known whether follitropin delta is excreted in human milk. The closely related agent, follitropin alfa, has been detected in milk in rats though REKOVELLE is not indicated during breastfeeding.

4.7 Effects on ability to drive and use machines
REKOVELLE is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
The most frequently reported adverse drug reactions during treatment with REKOVELLE are OHSS, headache, pelvic pain, nausea and fatigue. The frequency of these adverse reactions might decrease with repeated treatment cycles, as this has been observed in clinical trials.

ADRs from clinical trials
The table below (Table 2) displays the adverse reactions experienced in clinical trials by patients treated with REKOVELLE using the algorithm-based dosing regimen. Within each frequency grouping, adverse drug 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 Dizziness
Gastrointestinal disorders	Nausea	Diarrhoea Vomiting Constipation Abdominal discomfort[a]
Reproductive system and breast disorders	OHSS Pelvic pain[b]	Vaginal haemorrhage Breast discomfort[c]
General disorders and administration site conditions	Fatigue	

a Abdominal discomfort includes abdominal pain/distention.
b Pelvic pain includes pelvic discomfort and adnexa uteri pain.
c Breast discomfort includes breast pain, breast swelling, breast tenderness and/or nipple pain.

Description of selected adverse reactions

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.

Immunogenicity in terms of development of anti-FSH antibodies is a potential risk of gonadotropin therapy (see Section 5.1).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Sex hormones and modulators of the genital system, gonadotropins, ATC code: G03GA10

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

REKOVELLE 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. The glycosylation of FSH in REKOVELLE 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 FSH exposure and higher ovarian response (i.e. estradiol, inhibin B and follicular volume and number of follicles) were 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, for the majority of patients, 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.

Clinical efficacy and safety

ESTHER-1 clinical trial

The ESTHER-1 trial was a randomised, assessor-blinded, controlled trial in 1,326 IVF/ICSI patients. comparing the individualised dosing regimen of REKOVELLE (with fixed dose) to a standard dosing regimen of follitropin alfa filled-by-mass (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, 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 individualised 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 randomised and exposed

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

Ovarian response and total FSH dose

Excessive ovarian response leading to triggering with GnRH agonist occurred for fewer patients with the individualised REKOVELLE dosing regimen compared to the follitropin alfa dosing regimen ($p<0.05$). Low ovarian response leading to cycle cancellation occurred at comparable rates with REKOVELLE and follitropin alfa.

The probability of patients achieving 8-14 oocytes was increased for patients with low or high AMH treated with individualised REKOVELLE dosing regimen compared to follitropin alfa at a starting dose of 11 micrograms (150 IU) and adjustments during stimulation ($p<0.05$). The average REKOVELLE daily dose was 0.16 µg/kg. The ovarian response and total FSH dose overall and according to AMH concentration are displayed in Table 4.

Table 4 Ovarian response and gonadotropin use in ESTHER-1 trial

	REKOVELLE in an individualised dosing regimen	Follitropin alfa
All patients	N=665	N=661
Number of oocytes retrieved	10.0 ± 5.6	10.4 ± 6.5
Patients with 8-14 oocytes retrieved	43.3%	38.4%
Dose adjustments	0%	36.8%
Total dose (mcg)	90 ± 25	104 ± 34
AMH <15 pmol/L	N=297	N=306
Number of oocytes retrieved	8.0 ± 4.3	7.0 ± 3.9
Patients with <4 oocytes retrieved	11.8%	17.9%
Dose adjustments	0%	41.2%
Total dose (mcg)	104 ± 20	108 ± 40
AMH ≥15 pmol/L	N=368	N=355
Number of oocytes retrieved	11.6 ± 5.9	13.3 ± 6.9
Patients with ≥20 oocytes retrieved	10.1%	15.6%
Dose adjustments	0%	33.0%
Total dose (mcg)	79 ± 23	100 ± 26

Differences between REKOVELLE and follitropin alfa were statistically significant ($p<0.05$) for all parameters in the table with the exception of number of oocytes retrieved for all patients and total dose in the AMH <15 pmol/L category.
Ovarian response data are for patients with triggering of final follicular maturation.
Population: all randomised and exposed
mcg: micrograms

Safety – OHSS risk management

The incidence of patients who required preventive interventions for early OHSS, such as triggering with GnRH agonist or administration of dopamine agonist, was reduced by 50% in the REKOVELLE treated patients compared to the follitropin alfa treated patients ($p<0.05$). The risk of early OHSS and/or preventive interventions as well as the risk of early and late OHSS and/or preventive interventions was higher by increasing AMH with the standard follitropin alfa dosing regimen compared to the individualised REKOVELLE dosing regimen ($p<0.05$). OHSS risk management parameters are summarised in Table 5.

Table 5 OHSS risk management in ESTHER-1 trial

	REKOVELLE in an individualised dosing regimen (N=665)	Follitropin alfa (N=661)
Preventive interventions for early OHSS	2.3%	4.5%

Early OHSS and/or preventive interventions for early OHSS	4.7%	6.2%
Early moderate/severe OHSS and/or preventive interventions for early OHSS	3.6%	5.1%
Early and late OHSS and/or preventive interventions for OHSS	5.6%	8.0%
Early and late moderate/severe OHSS and/or preventive interventions for early OHSS	4.4%	6.7%

The OHSS risk was higher by increasing AMH with the standard follitropin alfa dosing regimen compared to the individualized REKOVELLE dosing regimen for all parameters in the table ($p<0.05$).
Population: all randomised and exposed

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.

ESTHER-2 clinical trial

Safety – immunogenicity
The ESTHER-2 trial included patients who participated in the ESTHER-1 trial who failed to achieve an ongoing pregnancy. These patients were eligible for cycle 2, and those who failed to achieve an ongoing pregnancy in cycle 2, were eligible for cycle 3. Patients with severe OHSS in a previous cycle, or patients with any clinically relevant change to any of the eligibility criteria or any clinically relevant medical history since the previous cycle were not eligible for participation in the trial. Treatment allocation to either REKOVELLE or follitropin alfa remained the same as in the ESTHER-1 trial. The treatment dose in both groups could be adjusted based on the ovarian response obtained in the previous cycle(s). Surplus blastocysts could be cryopreserved for use after trial completion. A post-trial follow-up evaluated the cryopreserved cycles initiated within one year after randomisation for patients participating in ESTHER-1, and within one year after start of stimulation of the last repeated controlled ovarian stimulation cycle for subjects enrolled in ESTHER-2.

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.

ESTHER-1 and ESTHER-2 clinical trials combined analyses

ESTHER-1 and ESTHER-2 trials combined include data from 1,027 controlled ovarian stimulation cycles and 692 frozen cycles. The 665 women randomised and exposed to REKOVELLE conducted 1,012 controlled ovarian stimulation cycles and initiated 341 frozen cycles, and the 661 women randomised and exposed to follitropin alfa conducted 1,015 treatment cycles and initiated 351 frozen cycles.

The overall live birth rate and the live neonate rate at 4 weeks after birth after fresh and frozen cycles were comparable for REKOVELLE and follitropin alfa for women who participated in the ESTHER trials.

Table 6 Cumulative live birth rate and live rate at 4 weeks after birth in ESTHER-1 and ESTHER-2 trials

		REKOVELLE in an individualised dosing regimen (N=665)	Follitropin alfa (N=661)	Rate difference [95% CI]
ESTHER-1 and ESTHER-2	Live birth rate	60.3%	61.1%	-0.6% [-5.8; 4.5]
	Live rate at 4 weeks after birth	60.3%	60.7%	-0.2% [-5.4;5.0]

Population: all randomised and exposed

The cumulative incidence of moderate/severe OHSS and/or preventive interventions for early OHSS across three controlled ovarian stimulation cycles were significantly lower for REKOVELLE compared to follitropin alfa ($p<0.05$), as displayed in Table 7.

Table 7 OHSS risk management in ESTHER-1 and ESTHER-2 trials

		REKOVELLE in an individualised dosing regimen (N=665)	Follitropin alfa (N=661)	Comparison Odds-ratio [95% CI]
ESTHER-1 and ESTHER-2	Any preventive intervention	2.9%	5.0%	0.56% [0.31; 0.99]
	Moderate/severe OHSS	2.1%	4.1%	0.50% [0.26; 0.97]
	Moderate/severe OHSS and/or preventive interventions	5.0%	8.2%	0.59% [0.38; 0.92]

Population: all randomised and exposed

<u>BEYOND Phase 3b trial, 000304</u>

In an open-label, controlled trial 435 IVF/ICSI patients with AMH ≤ 35 pmol/L were randomised to either individualised REKOVELLE dosing in a protocol using down-regulation with a GnRH agonist or to a GnRH antagonist. The maximum allowed REKOVELLE dose was 12 micrograms. The primary endpoint was number of oocytes retrieved. The mean number of oocytes retrieved among patients who started controlled ovarian stimulation with REKOVELLE was 11.1± 5.9 in the GnRH agonist cycle compared to 9.6 ± 5.5 in the GnRH antagonist cycle. The mean number of stimulation days in the GnRH agonist cycle was 10.4 ± 1.9 days compared to 8.8 ± 1.8 days in the GnRH antagonist cycle. The live birth rate per started cycle was 35.1% in the GnRH agonist cycle compared to 28.9% in the GnRH antagonist cycle. The proportion of patients with early OHSS was 4.0% in the GnRH agonist cycle and 2.5% in the GnRH antagonist cycle, and the proportion of patients with early moderate/severe OHSS was 1.5% in the GnRH

agonist cycle and 2.5% in the GnRH antagonist cycle. The proportion of patients with late OHSS was 2.0% in the GnRH agonist cycle and 2.9% in the GnRH antagonist cycle, and the proportion of patients with late moderate/severe OHSS was 1.5% in the GnRH agonist cycle and 3.0% in the GnRH antagonist cycle.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of REKOVELLE 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 REKOVELLE is inversely related to the body weight, which supports individualised dosing based on body weight. Follitropin delta leads to greater exposure than follitropin alfa.

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 REKOVELLE increases proportionally with the dose.

Elimination

Following intravenous administration, the clearance of REKOVELLE 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 REKOVELLE with follitropin alfa following daily subcutaneous administration of equal doses of IUs for 7 days, revealed that the apparent clearance is 1.6 fold lower and accordingly the AUC and C_{max} are 1.7-fold and 1.6-fold higher for REKOVELLE than for follitropin alfa. REKOVELLE is expected to be eliminated similarly to other follitropins, i.e. mainly by the kidneys. The fraction of REKOVELLE excreted unchanged in the urine was estimated to 9%.

5.3 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 REKOVELLE resulted in pharmacological or exaggerated pharmacological actions. REKOVELLE had a negative effect on fertility and early embryonic development in rats when administered in doses ≥0.8 µg/kg/day which is above the recommended maximal dose in humans. Since REKOVELLE is contraindicated during pregnancy, these observations are of limited clinical significance**.**

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol
Polysorbate 20
L-methionine
Sodium sulfate decahydrate
Disodium hydrogen phosphate dodecahydrate
Concentrated phosphoric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
3 years.

After first injection: 28 days when stored at or below 30°C.

6.4 Special precautions for storage
Store in a refrigerator (2°C – 8°C).

Do not freeze.

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.

For storage conditions after first use of the medicinal product, see section 6.3.

6.5 Nature and contents of container
REKOVELLE solution for injection in pre-filled pen 12 micrograms/0.36 mL
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 solution for injection in pre-filled pen 36 micrograms/1.08 mL
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 9 injection needles (stainless steel).

REKOVELLE solution for injection in pre-filled pen 72 micrograms/2.16 mL
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 15 injection needles (stainless steel).

6.6 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.

7 MANUFACTURER
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8 DATE OF REVISION

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