NEW ZEALAND DATA SHEET

Rekovelle solution for injection in pre-filled multidose pen

Follitropin delta

1 PRODUCT NAME

REKOVELLE 12 micrograms/0.36 mL solution for injection in a pre-filled multidose pen.

REKOVELLE 36 micrograms/1.08 mL solution for injection in a pre-filled multidose pen.

REKOVELLE 72 micrograms/2.16 mL solution for injection in a pre-filled multidose pen.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled multidose pen contains 12 micrograms follitropin delta* in 0.36 mL solution.

One pre-filled multidose pen contains 36 micrograms follitropin delta* in 1.08 mL solution.

One pre-filled multidose pen contains 72 micrograms follitropin delta* in 2.16 mL solution.

For all products, 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.

Excipient(s) with known effect:

This medicinal product contains less than 1mmoL (23mg) sodium per dose.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection in a pre-filled multidose pen with injection needles.

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 Dose and method of administration

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

Posology

The dosage of REKOVELLE is individualised 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 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 (i.e. within the last 12 months) determination of AMH concentration measured by one of the following diagnostic test from Roche: ELECSYS AMH Plus immunoassay from Roche (i.e assay used in clinical development trials) or, alternatively, the Access® AMH Advanced immunoassay from Beckman Coulter.

The dosing recommendations (based on AMH concentration and body weight) are presented in Table 1. These dosing recommendations rely on the use of the Roche Elecsys AMH Plus or the Beckman Coulter Access AMH Advanced immunoassays. The use of other AMH assays for this purpose is not recommended, as there is currently no standardisation of available AMH assays.

Patients with low AMH levels are likely to have low ovarian reserve.

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 by 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 based on AMH concentration and body weight.

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

[a] AMH concentration measured with either the Elecsys® AMH Plus immunoassay from Roche or the ACCESS AMH Advance immunoassay from Beckman Coulter.

[b] Up to a maximum daily dose of 12 micrograms, for the first treatment cycle. In subsequent treatment cycles following an inadequate initial response, the dose may be adjusted (see below) to a maximum of 24 micrograms.

Treatment with REKOVELLE should be initiated day 2 or 3 after start of menstrual bleeding, and continue until adequate follicular development (≥3 follicles ≥17 mm) has been achieved, as assessed by monitoring with ultrasound alone or in combination with measurement of serum oestradiol 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 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. In these patients, administration of a GnRH agonist instead of hCG 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.

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 is 33% lower than the dose used in the cycle where OHSS or risk of OHSS occurred.

The maximum daily dose is 24 micrograms.

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 4.4).

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 5.1).

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

REKOVELLE is intended for subcutaneous use, preferably in the abdominal wall. The first injection of REKOVELLE 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 administering a prescribed dose of REKOVELLE pre-filled injection pen, see the "Instructions for Use" in the pack.

The solution should not be administered if it contains particles of is not clear. Any unused solution should be discarded no later than 28 days after the first injection. Discard used needles immediately after each injection (see section 6.6).

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

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

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 other assays than the ELECSYS AMH Plus immunoassay from Roche 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 OHSS. Adherence to the REKOVELLE dose and regimen of administration and careful monitoring of therapy will minimise 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. 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.

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.

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, i.e. essentially "sodium free".

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed with REKOVELLE. Clinically significant interactions with other medicinal products have neither been reported during REKOVELLE therapy, nor are expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

REKOVELLE is contraindicated 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 5.3).

Breast-feeding

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. REKOVELLE is contraindicated during breast-feeding

Fertility

REKOVELLE is indicated for use in infertility (see section 4.1).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

Table 2 combines all three controlled ovarian stimulation (COS) cycles in the ESTHER trials and thus provides the most frequent adverse events based on 1,012 treatment cycles with REKOVELLE and 1,015 treatment cycles with GONAL-F in the phase 3 program conducted in IVF/ICSI patients.

Table 2: Adverse Events (≥ 2%) in completed phase 3 trials in IVF/ICSI patients – Cycle Level†.

MedDRA system organ class / preferred term	**REKOVELLE (N‡=1012 cycles)**			**GONAL-F (N‡=1015 cycles)**		
	n*	**%^**	**E****	**n ***	**%^**	**E****
Any adverse events	415	41.0%	1423	387	38.1%	1428
Gastrointestinal disorders	100	9.9%	165	84	8.3%	173
Nausea	34	3.4%	43	34	3.3%	46
Constipation	23	2.3%	26	26	2.6%	32
General disorders and administration site conditions	55	5.4%	90	50	4.9%	82
Fatigue	24	2.4%	28	22	2.2%	34
Infections and infestations	77	7.6%	86	58	5.7%	70
Respiratory tract infection	28	2.8%	30	21	2.1%	22
Injury, poisoning and procedural complications	108	10.7%	146	108	10.6%	160
Procedural pain	61	6.0%	71	64	6.3%	82
Nervous system disorders	130	12.8%	208	120	11.8%	210
Headache	113	11.2%	167	104	10.2%	159
Pregnancy, puerperium and perinatal conditions	150	14.8%	197	157	15.5%	202
Biochemical pregnancy	44	4.3%	47	34	3.3%	37
Haemorrhage in pregnancy	43	4.2%	47	39	3.8%	47
Abortion spontaneous	40	4.0%	42	42	4.1%	43
Vomiting in pregnancy	39	3.9%	45	41	4.0%	51
Reproductive system and breast disorders	167	16.5%	273	176	17.3%	316
Pelvic pain	60	5.9%	71	53	5.2%	76
Pelvic discomfort	42	4.2%	52	35	3.4%	52
Ovarian hyperstimulation syndrome	28	2.8%	28	40	3.9%	41
Adnexa uteri pain	29	2.9%	37	26	2.6%	31

† Aggregated adverse event data from all COS cycles in ESTHER-1 and ESTHER-2 trials

‡ N = total number of COS cycles

The most frequently reported adverse drug reactions (ADR) during treatment with REKOVELLE are headache, pelvic discomfort, ovarian hyperstimulation syndrome, pelvic pain, nausea, adnexa uteri pain and fatigue. None of these ADRs have been reported with an incidence rate of more than 5%. The frequency of these adverse reactions might decrease with repeated treatment cycles, as this has been observed in clinical trials.

Tabulated list of adverse reactions

The table below (Table 2) displays the adverse drug reactions in patients treated with REKOVELLE in the pivotal clinical trials according to MedDRA system organ class and frequency as follows: common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Adverse drug reactions in pivotal clinical trials

MeDRA System Organ Class (SOC)	**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
Reproductive system and breast disorders	OHSS Pelvic pain Adnexa uteri pain Pelvic discomfort	Vaginal haemorrhage Breast pain Breast tenderness
General disorders and administration site conditions	Fatigue	

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.

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

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital systems, gonadotropins, and other ovulation stimulants

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. Differences in glycosylation profile, sialic acid pattern and isoform profile have been documented between REKOVELLE 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 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, carries additional linkages between carbohydrates such as bisecting N-acetylglucosamine and antennary fucose, and has a higher proportion of tetra-antennary structures and higher overall sialic acid content than CHO-derived recombinant FSH.

Pharmacodynamic effects compared to follitropin alfa

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) was observed in patients 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 trial data suggest that a daily dose of 10.0 micrograms [95% CI 9.2; 10.8] of REKOVELLE provides, for the majority of patients, an ovarian response (i.e. oocytes retrieved, follicles ≥ 12 mm and estradiol) similar to that obtained with 150 IU/day follitropin alfa.

The recommended doses of REKOVELLE in micrograms are specific to REKOVELLE and are not applicable to other recombinant FSH preparations.

Factors affecting response

The number of oocytes retrieved increases with the dose of REKOVELLE and serum concentration of women's AMH hormone. 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 4.2).

Clinical efficacy and safety

The ESTHER-1 trial was a randomised, assessor-blinded, controlled trial in 1,326 IVF/ICSI patients. The trial compared the individualised dosing regimen of REKOVELLE where the daily dose is established for each patient and fixed throughout stimulation with no adjustments (see section 4.2) 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. 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 4 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 overall average number of oocytes retrieved was similar for patients treated with REKOVELLE and follitropin alfa, with more patients treated with REKOVELLE achieving 8-14 oocytes in comparison 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 micrograms/kg. The ovarian response and total FSH dose overall and according to AMH concentration are displayed in Table 4.

Table 5 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 (micrograms)	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 (micrograms)	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 (micrograms)	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

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). Early OHSS and/or preventive interventions as well as early and late OHSS and/or preventive interventions occurred less frequently with the individualised REKOVELLE dosing regimen compared to the standard follitropin alfa dosing regimen (p<0.05). OHSS risk management parameters are summarised in Table 5.

Table 6 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%

Differences between REKOVELLE and follitropin alfa were statistically significant (p<0.05) for all parameters in the table.

Population: all randomised and exposed

In ovulatory patients with polycystic ovaries, 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.

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.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of REKOVELLE has been investigated in healthy female subjects and in in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) patients undergoing controlled ovarian stimulation (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 are inversely related to the body weight, which supports individualized 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 follitropin delta increases proportionally with the dose.

Elimination

Following intraveneous 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 AUC and Cmax 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol

Polysorbate 20

Methionine

Sodium sulphate decahydrate

Dibasic sodium phosphate dodecahydrate

Phosphoric acid, concentrated (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

In use: 28 days when stored at or below 25 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

Before use, store in the original package in order to protect from light.

Within its shelf life, REKOVELLE may be removed from the refrigerator, without being refrigerated again, and stored at or below 25 °C for up to 3 months. It must be discarded afterwards.

After the first injection: the pre-filled pen can be stored at or below 25 °C and it must be discarded after 28 days. Reattach the pen cap after each injection.

Each REKOVELLE pre-filled injection pen is for individual patient use only.

6.5 Nature and contents of container

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

Pre-filled injection pen containing an integrated 3 mL multidose cartridge (Type I glass) with a plunger (halobutyl rubber) and a crimp cap (aluminium) with an inlay (rubber). Each cartridge contains 12 micrograms follitropin delta in 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

Pre-filled injection pen containing an integrated 3 mL multidose cartridge (Type I glass) with a plunger (halobutyl rubber) and a crimp cap (aluminium) with an inlay (rubber). Each cartridge contains 36 micrograms follitropin delta in 1.08 mL of solution.

Pack size of 1 pre-filled pen and 9 injection needles (stainless steel).

REKOVELLE 72 micrograms/2.16 mL solution for injection in pre-filled pen

Pre-filled injection pen containing an integrated 3 mL multidose cartridge (Type I glass) with a plunger (halobutyl rubber) and a crimp cap (aluminium) with an inlay (rubber). Each cartridge contains 72 micrograms follitropin delta in 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 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
Telephone: 09 377 3336

9 DATE OF FIRST APPROVAL

30 Jan 2020

10 DATE OF REVISION OF THE TEXT

May 2022[CCDS 30994 Ver 2.0 dated 01 Dec 2017]

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Addition of AMH Advanced immunoassay from Beckman Coulter as an alternative in-vitro diagnostic test for determination of anti-Müllerian hormone
4.3	Addition of pregnancy and lactation as contraindications
4.6	Update to this section to align with pregnancy and lactation as a contraindication
4.8	Update to adverse event tables
5.1	Rewording of section on 'Pharmacodynamic effects compared to follitropin alfa' to reflect new information
6.5	Change to number of injection needles provided in packs of REKOVELLE 36 microgram and 72 microgram product presentations
Multiple sections	Minor editorial changes