AUSTRALIAN PRODUCT INFORMATION - REKOVELLE® (follitropin delta*) solution for injection pre-filled multidose pen

1 NAME OF THE MEDICINE

Follitropin delta*

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

REKOVELLE 12 micrograms: contains 12 micrograms follitropin delta (rhu) in 0.36 mL. One pre-filled multidose pen contains 12 micrograms follitropin delta (rhu)* in 0.36 mL solution.

REKOVELLE 36 micrograms: contains 36 micrograms follitropin delta (rhu) in 1.08 mL. One pre-filled multidose pen contains 36 micrograms follitropin delta (rhu)* in 1.08 mL solution.

REKOVELLE 72 micrograms: contains 72 micrograms follitropin delta (rhu) in 2.16 mL. One pre-filled multidose pen contains 72 micrograms follitropin delta (rhu)* in 2.16 mL solution.

For all products, one mL of the solution contains 33.3 micrograms of follitropin delta (rhu).

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

REKOVELLE (follitropin delta) solution for injection includes the following excipients: phenol, polysorbate 20, methionine, sodium sulfate decahydrate, dibasic sodium phosphate dodecahydrate, phosphoric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

3 PHARMACEUTICAL FORM

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

The average molecular weights of the glycosylated α and β subunits are approximately 15,200 and 18,500 Daltons (Da), respectively. Thus, approximately 40% of the total molecular weight of the molecule is due to glycosylation. No animal-derived materials are used in the REKOVELLE manufacturing processes.

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

Clear and colourless solution. The pH of the solution is 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. Patients must be educated on how to use the REKOVELLE injection pen and to perform injections.

The dosage of REKOVELLE is individualised for each patient to obtain an ovarian response with favourable safety/efficacy profile (see **Section 5.1 – PHARMACODYNAMIC PROPERTIES**). REKOVELLE is dosed in micrograms and not in international units (IU) of biological activity (see **Section 5.1 – 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, 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 tests: 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, 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

AMH concentration[a] (pmol/L)	Daily dose fixed throughout stimulation[b]
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 Advanced 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.

Dosing with REKOVELLE should be initiated day 2 or 3 after start of menstrual bleeding, and continue until adequate follicular development has been achieved as assessed by monitoring with ultrasound alone or in combination with measurement of serum 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 ovarian response at risk of ovarian hyperstimulation syndrome (OHSS), 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. The maximum daily dose is 24 micrograms.

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.

There is no clinical trial experience with REKOVELLE in the long GnRH agonist protocol (see **Section 5.1 – PHARMACODYNAMIC PROPERTIES**).

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

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

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.

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 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 or is not clear. Any unused solution must be discarded no later than 28 days after first injection. Discard used needles immediately after each injection.

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in **Section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION**
- 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 oestradiol levels, on a regular basis. The dose of REKOVELLE is individualised for each patient to obtain an ovarian response with a favourable safety/efficacy profile. There may be a degree of inter-patient 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 hyperprolactinaemia, and the appropriate specific treatment should be given.

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.

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/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 (23 mg) sodium per dose

Use in women over 40 years of age

There is limited experience in the use of REKOVELLE in women over 40 years of age.

Use in the elderly

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

Paediatric use

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

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed with REKOVELLE.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

REKOVELLE is indicated for use in infertility (see **Section 4.1 - THERAPEUTIC INDICATIONS**).

Use in pregnancy

(Category D)

REKOVELLE is contraindicated during pregnancy (see **Section 4.3 - CONTRAINDICATIONS**). 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.

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. REKOVELLE is contraindicated during breast-feeding (see **Section 4.3 - CONTRAINDICATIONS**).

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

* n = number of subjects reporting at least one adverse event

^ % = ratio of number of subjects reporting at least one adverse event relative to the total number of COS cycles, expressed as a percentage [(n/N) x 100]

** E = number of adverse events reported across all COS cycles (within a cycle a patient may have reported the same adverse event more than once)

The most frequently reported adverse drug reactions during treatment with REKOVELLE in pivotal clinical trials (1,012 cycles) are headache (4.2%), pelvic discomfort (2.9%), ovarian hyperstimulation syndrome (2.3%), pelvic pain (1.6%), nausea (1.4%), adnexa uteri pain (1.4%) and fatigue (1.2%).

The table below (Table 3) displays the adverse drug reactions in patients treated with REKOVELLE in the pivotal clinical trials according to system organ class and frequency; common (≥ 1/100 to <1/10) and uncommon (≥ 1/1,000 to <1/100). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions in pivotal clinical trials

MedDRA System Organ Class (SOC)	**Common (≥ 1/100 and < 1/10)**	**Uncommon (≥ 1/1000 and < 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 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 effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The effect of an overdose in humans is unknown, nevertheless, there is a risk that OHSS may occur (see **Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

For information on the management of overdose, contact the Poisons Information Centre on 131 126 (Australia).

Advise your patients to immediately contact their doctor or the Poisons Information Centre (telephone 131 126) if they are concerned that they have given themselves too much REKOVELLE.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Sex hormones and modulators of the genital systems, gonadotropins and other ovulation stimulants, 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. 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 which are 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 FSH exposure and higher ovarian response (i.e. estradiol, inhibin B and follicular volume) were observed in patients after administration of REKOVELLE compared to follitropin alfa. As the rat 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 influencing response

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

The ESTHER-1 trial was a randomised, assessor-blinded, controlled trial in 1,326 IVF/ICSI patients comparing the individualised dosing regimen (see **Section 4.2 – DOSE AND METHOD OF ADMINISTRATION)** 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). The patients were up to 40 years of age and had regular menstrual cycles presumed to be ovulatory. As for other clinical trials of gonadotropins, a number of inclusion and exclusion criteria were applied in recruiting the ESTHER trial population. For example, patients were excluded if the following were present: endometriosis stage III–IV, history of recurrent miscarriage, and use of hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomisation. Polycystic ovarian syndrome (PCOS) patients with anovulatory disorders have not been studied.

Single blastocyst transfer on day 5 was compulsory with the exception of patients aged 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 4.

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 5.

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 6.

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.

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* fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) patients undergoing controlled ovarian stimulation (COS). Following repeated daily subcutaneous administration, REKOVELLE reaches steady-state within 6 to 7 days with a three-fold higher concentration compared with the concentration after the first dose. Circulating levels of REKOVELLE are inversely related to the body weight, which supports individualised dosing based on body weight.

Within the therapeutic dose range, exposure to REKOVELLE increases proportionally with the dose.

Absorption

After a single subcutaneous administration of REKOVELLE, the time to maximum concentration is approximately 20 hours.

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.

Metabolism

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 be 9%.

Excretion

Following intravenous administration, the clearance of REKOVELLE is 0.3 L/h. The terminal 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, respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted. The primary structure of follitropin delta is identical to endogenous FSH. As a large molecular weight protein, follitropin delta is not expected to interact with DNA or other chromosomal material.

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of follitropin delta.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to **Section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION**.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

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 and must be discarded afterwards.

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

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 pen cap after each injection.

6.5 NATURE AND CONTENTS OF CONTAINER

REKOVELLE is a clear and colourless solution for injection presented in a pre-filled multidose pen with a dose selection knob, display window and cap. Each pen contains an integrated non-replaceable cartridge containing the solution for injection.

12 micrograms:

Pre-filled injection pen containing an integrated 3 mL cartridge (Type I glass) with a plunger (halobutyl rubber), an aluminium crimp cap with a rubber inlay and 12 micrograms follitropin delta (rhu) in 0.36 mL of solution for injection.
Pack of 1 pre-filled pen and 3 injection needles (stainless steel).

36 micrograms:

Pre-filled injection pen containing an integrated 3 mL cartridge (Type I glass) with a plunger (halobutyl rubber), an aluminium crimp cap with a rubber inlay and 36 micrograms follitropin delta (rhu) in 1.08 mL of solution for injection.
Pack of 1 pre-filled pen and 9 injection needles (stainless steel).

72 micrograms:

Pre-filled injection pen containing an integrated 3 mL cartridge (Type I glass) with a plunger (halobutyl rubber), an aluminium crimp cap with a rubber inlay and 72 micrograms follitropin delta (rhu) in 2.16 mL of solution for injection.
Pack of 1 pre-filled pen and 15 injection needles (stainless steel).

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure

Follitropin delta is a heterodimer composed of one α and one β subunit. The amino acid sequence and the glycosylation sites of the mature α and β subunits are:

FSH subunit α

1 APDVQDCPEC TLQENPFFSQ PGAPILQCMG CCFSRAYPTP LRSKKTMLVQ K***N***VTSESTCC

61 VAKSYNRVTV MGGFKVE***N***HT ACHCSTCYYH KS

FSH subunit β

1 NSCELT***N***ITI AIEKEECRFC ISI***N***TTWCAG YCYTRDLVYK DPARPKIQKT CTFKELVYET

61 VRVPGCAHHA DSLYTYPVAT QCHCGKCDSD STDCTVRGLG PSYCSFGEMK

CAS Number

146479-72-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine

8 SPONSOR

Ferring Pharmaceuticals Pty Ltd
Suite 2, Level 1, Building 1
20 Bridge Street
Pymble NSW 2073
Australia

Toll Free: 1800 337 746

9 DATE OF FIRST APPROVAL

14 September 2017

10 DATE OF REVISION

9 May 2022

For the most current approved PI, please refer to https://www.ebs.tga.gov.au/ or http://www.ferring.com.au/

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
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