Taiwan Food and Drug Administration

Assessment Report

Trade Name：
樂可孕注射筆 12 微克/0.36 毫升 /
REKOVELLE 12 μg/0.36 mL solution for injection in pre-filled pen
樂可孕注射筆 36 微克/1.08 毫升 /
REKOVELLE 36 μg/1.08 mL solution for injection in pre-filled pen
樂可孕注射筆 72 微克/2.16 毫升 /
REKOVELLE 72 μg/2.16 mL solution for injection in pre-filled pen

Active Ingredient：Follitropin delta

License Number：MOHW-BI 001187
MOHW-BI 001188
MOHW-BI 001189

Applicant：輝凌藥品股份有限公司

Approval Date：111/03/08

Indication：
女性進行人工生殖技術(ART)，如體外授精(IVF)、單精子胞漿內注射(ICSI)週期時，於受控制下刺激卵巢以誘發多個濾泡發育。
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.

Background Information

Trade Name	樂可孕注射筆 12 微克/0.36 毫升 / REKOVELLE 12 µg/0.36 mL solution for injection in pre-filled pen 樂可孕注射筆 36 微克/1.08 毫升 / REKOVELLE 36 µg/1.08 mL solution for injection in pre-filled pen 樂可孕注射筆 72 微克/2.16 毫升 / REKOVELLE 72 µg/2.16 mL solution for injection in pre-filled pen
Active Ingredient(s)	Follitropin delta
Applicant	輝凌藥品股份有限公司
Dosage Form & Strengths	注射劑 12 µg/0.36 mL 注射劑 36 µg/1.08 mL 注射劑 72 µg/2.16 mL
Indication	女性進行人工生殖技術(ART)，如體外授精(IVF)、單精子胞漿內注射(ICSI)週期時，於受控制下刺激卵巢以誘發多個濾泡發育。 目前臨床試驗證據主要來自對 REKOVELLE 使用 GnRH 拮抗劑治療療程的研究。 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.
Posology	詳如仿單
Pharmacological Category **ATC Code**	G03GA10

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Follitropin delta, also known as FE 999049, is a recombinant follicle-stimulating hormone (rFSH) which plays a key role in fertility. FE 999049 is expressed from a host cell line of human origin, and is a glycoprotein which is composed of two non-covalently bound

polypeptide chains, denoted alfa (α) and beta (β). The average molecular weights of the glycosylated α and β subunits are approximately 15,200 and 18,500 Daltons, respectively. The amino acid sequence of FE 999049 is identical to the endogenous human FSH sequence for both α and β subunits, and to that of existing Chinese hamster ovary (CHO)-derived recombinant FSH products. Differences have been observed in the glycosylation profiles between FE 999049 and CHO-derived rFSH products.

Manufacturing

The DS is manufactured in accordance with GMP. The manufacturing process of FE 999049 DS consists of cell culture, harvest, purification, and buffer-adjustment. A production run begins with WCB vial thawed, through the cell culture expansion and harvest of the production culture, followed by purification by a series of chromatography steps. Additional steps are introduced for inactivation/removal of the potential viral contaminants. The DS solution is then adjusted and filtered into storage container.

Controls

- Sufficient details are provided on the source and history of the cell substrate. The generation of the production cell line and the expression vectors is described in detail.
- The details of raw and starting materials used in the manufacturing process as well as quality standards (compendial monograph or in-house specifications) are presented.
- The in-process controls and critical process parameter are provided sufficiently.
- The results of the virus clearance study demonstrate that the log reduction factors obtained for each of the viruses sufficiently mitigate the risk of adventitious virus contamination of the FE 999049 DS.
- The risk for transmission of TSE/BSE is inferred to be negligible.

Process validation

The validation of the manufacturing process was carried out on full-scale PPQ lots. Results obtained from these batches meet the pre-defined criteria and demonstrate the process consistency.

Characterization

The followings are included in characterization studies：

- Physicochemical characterization: primary sequences, post-translational modifications, size variants, sequence variants, charge variants and higher-order structure.
- Biological and immunochemical characterization: *in-vivo* (rat) and *in-vitro* cell-based assay.
- The potential produced- and process-related impurities have been analyzed and are considered sufficiently controlled.

DS specification

The release testing of FE 999049 includes identity, appearance, purity, potency, pH, content

and contaminants. Descriptions of the non-compendial analytical procedures validation summaries are provided. The proposed specifications of DS are considered adequate and acceptable.

Reference materials

The qualification reports of current RSs have been provided.

Stability

The stability data from production batches revealed that the DS is stable under storage condition for 36 months at −20±5°C.

2.1.2 Drug product

REKOVELLE is available as a sterile 33.3 µg/mL concentrate for solution in cartridge assembled into an injection pen in three strengths: 12 µg, 36 µg and 72 µg. The excipients for DP solution contain Phenol, Polysorbate 20, L-methionine, Sodium sulphate decahydrate, Disodium phosphate dodecahydrate, Phosphoric acid concentrated (for pH adjustment), Sodium hydroxide (for pH adjustment), and water for injection.

Manufacturing

The manufacturing process consists of DS thawing, mixing the DS with a formulated excipient solution, bioburden reduction, sterile filtration followed by an aseptic filling into sterile cartridges. Then, FE 999049 DP cartridges are assembled into the FE 999049 injection pen forming a single integral unit.

Controls

The critical process parameters and in-process control tests have been provided properly.

Process validation and/or evaluation

The process validation summaries on three consecutive production batches are provided. The aseptic processing and the suitability of the equipment are ensured.

DP Specification

The release testing of FE 999049 DP includes identity, appearance, purity, osmolality, potency, pH, particulate matter, contaminants, and extractable volume. The proposed specifications of DP are considered adequate and acceptable. Batch analysis data of finished product batches are provided, and the results reveal a satisfactory batch to batch consistency.

Reference materials

The qualification reports of current RSs have been provided.

Stability of the DP

The long-term and accelerated stability data for DP are provided. The photo-stability and Freeze/Thaw studies were also performed on DP batches. Overall, the stability data provided

could support the proposed shelf-life of 36 months when the DP is stored at the recommend condition (5±3°C) and the secondary packaging carton could provide adequate protection from light. The in-use stability results showed that the DP are stable for 28 days at or below 30°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In *in vitro* pharmacology, FE 999049 and GONAL-F (follitropin alfa) showed very similar activities, including almost the same Ki values of these two drugs and comparable Ki and K_D values of FE 999049 in [Propionyl-^{3}H]-FE 999049 binding assay. The comparable potencies of FE 999049 DP and GONAL-F were shown in the direct measurement of intracellular cyclic adenosine monophosphate (cAMP) accumulation. In a study, women's granulosa cells from preovulatory follicles were incubated with FE 999049 or GONAL-F for 24 hours. The results showed that the expression of 3ß-HSD and inhibin A and the secretion of progesterone and inhibin A were similar between FE 999049 and GONAL-F. Regarding safety pharmacology, FE 999049 showed no effects in an hERG testing and cardiovascular, CNS and respiratory studies.

2.2.2 Toxicological Studies

In single-dose toxicology studies in mice or rats, no death occurred at the highest dose of 290 µg/kg, which was about 1000 times the anticipated human therapeutic dose. In a 14-day DRF study in rats and a maximum tolerated dose (MTD) study in cynomolgus monkeys, there were no adverse, off-target effects, but exaggerated pharmacological effects were observed in both species, including increased absolute and relative ovary weight. The NOAEL of the rat DRF study and the monkey's MTD were the high doses of 145 and 290 µg/kg/day, respectively. No systemic off-target toxicity has been observed in rat or monkey 4-week studies. All findings are attributable to the pharmacological effects of FE 999049. Most changes were entirely or partly reversible at the end of the treatment-free period.

After 28-day FE 999049 treatment in rats and monkeys, ADAs were generated and could be detected at 4 weeks recovery duration. In rats' fertility and early embryonic development studies, the expected pharmacological FSH effects were noted after subcutaneous administration of FE 999049. Since FE 999049 is contraindicated in a clinical setting with pregnancy or breastfeeding, no teratology or pre- and post-natal studies were performed. No genotoxicity and carcinogenicity studies have been conducted since FE 999049 is an endogenous protein hormone. A study of neutralizing antibody formation in rats demonstrated a high antibody response after 6-8 weeks of treatment with FE 999049.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Follitropin delta (FE 999049) is absorbed slowly after both single and multiple SC

administration to healthy female subjects, with the median T_{max} ranging from 10 to 24 hours. The mean absolute bioavailability of FE 999049 administered SC was determined to be 64%, which is close to the 60% found for follitropin alfa. Single SC administration of increasing doses to healthy female subjects indicated dose proportionality of C_{max} and AUC over a wide dose range of 12-24 µg. The mean V_z/F after SC injection was approximately 25 L and mean V_{ss} after IV administration was 9 L. FE 999049 clearance after IV administration was 0.3 L/h.

No dedicated investigations on the metabolism and excretion of FE 999049 have been performed. FE 999049 is thought to be metabolized like other FSH preparations, predominantly in the kidneys but also in the liver. The observation that the terminal half-life following single SC administration was longer than after IV administration (38 versus 24 hours) indicates that the absorption rate is the rate-limiting step for elimination. Approximately 9% of the dose of FE 999049 was excreted unchanged in the urine, indicating that renal excretion of intact FE 999049 does not play a major role in the elimination.

2.3.2 Interaction Studies

No clinical or non-clinical drug-drug interaction studies have been performed. Because therapeutic proteins are not metabolized by CYP450 enzymes, it is generally perceived that they are free from metabolism-based drug interactions and that therapeutic protein-drug interactions are clinically insignificant.

2.3.3 Special Populations

No studies in special populations have been performed. The effects of eGFR, ALT and bilirubin have been evaluated using the population PK model for the phase 2 and phase 3 trials. Based on provided PK data (effect of eGFR rate on ratio exposure FE 999049), it could be agreed that mild renal impairment does not have a marked effect on the systemic exposure to FE 999049. As no data or very few are available for respectively severe and moderate renal impaired patients, no conclusions can be drawn on the recommended use in these subgroups. Based on the provided data, the elevated levels of hepatic function markers (AST/ALT and bilirubin) appears to not have a marked effect on the systemic exposure to FE 999049. As the studied population included mainly patients with normal hepatic function and only few mild hepatic impaired patients, no conclusions could be made regarding moderate and severe hepatic impaired subgroups.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

A total of three Phase 3 clinical studies were evaluated and supported the efficacy of REKOVELLE® (follitropin delta) solution for injection in pre-filled pen with the therapeutic indication in 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.

Non-inferiority of REKOVELLE to GONAL-F was demonstrated for the two co-primary endpoints, ongoing pregnancy rate and ongoing implantation rate, for both the PP and mITT populations in Study [ESTHER-1]. The ongoing pregnancy rate (defined as at least one intrauterine viable fetus 10-11 weeks after transfer) was 30.7% and 31.6% in the REKOVELLE and GONAL-F groups for the mITT population (difference (95% CI): -0.9% (-5.9, 4.1)), and 31.8% and 32.6% for the PP population (difference (95% CI): -0.9% (-6.0, 4.3)). The ongoing implantation rate (defined as the number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of blastocysts transferred) was 35.2% and 35.8% in the REKOVELLE and GONAL-F groups for the mITT population (difference (95% CI): -0.6% (-6.1, 4.8)), and 36.2% and 36.9% for the PP population (difference (95% CI): -0.9% (-6.5, 4.7)). The lower bounds of the 95% CI were all above the pre-specified non-inferiority limit of -8.0% for both co-primary endpoints and for both the PP and mITT populations.

Non-inferiority of REKOVELLE to GONAL-F was demonstrated for the primary endpoint, ongoing pregnancy rate, for both the PP and FAS populations in Study [Pan-Asian]. The ongoing pregnancy rate (defined as at least one intrauterine viable fetus 10-11 weeks after transfer) was 31.3% and 25.7% in the REKOVELLE and GONAL-F groups for the FAS population (difference (95% CI): 5.4% (-0.2, 11.0)), and 30.1% and 25.2% for the PP population (difference (95% CI): 4.8% (-0.8, 10.4)). The lower bounds of the 95% CI were both above the pre-specified non-inferiority limit of -10.0% for both the PP and FAS populations.

Non-inferiority of REKOVELLE to FOLLISTIM with regard to number of oocytes retrieved was demonstrated for the FAS population in Japan Study [000273]. The mean (SD) number of oocytes retrieved for the FAS population was 9.3 (5.4) in the REKOVELLE group and 10.5 (6.1) in the FOLLISTIM group (difference (95% CI): -1.2 (-2.3, -0.1)). The lower bound of the 95% CI was above the pre-specified non-inferiority limit of -3.0.

2.4.2 Safety Results

The incidence rate of total AEs was comparable between the FE999049 groups and the active comparator groups in these phase 3 trials except Trial 000273, which the AE incidence of the FE999049 group was 10% lower than the Follistim group. The SAE incidence was low (1~2%) at both groups among these phase 3 trials, except Trial 000145. In Trial 000145, the SAE incidence was 6.0% in the FE999049 group and 3.5% in the Gonal-F group. The incidence of AEs leading to discontinuation in the REKOVELLE groups was lower than the comparator groups.

The most frequently reported adverse drug reactions (ADR) during treatment with REKOVELLE were headache, pelvic discomfort, ovarian hyperstimulation syndrome, pelvic pain, nausea, adnexa uteri pain and fatigue. Pregnancy-related conditions (such as ectopic pregnancy, threatened abortion, and spontaneous abortion) and OHSS (ovarian hyperstimulation syndrome) were the most frequently reported serious adverse events. In all phase 3 trials, the most common AEs leading to treatment discontinuation was OHSS with the incidence rate slightly higher in the comparator groups than in the FE999049 groups. There were no clinically relevant changes in the chemistry parameters, physical examination or GYN examination and vital signs between two treatment groups in either trial.

The incidence of treatment-induced anti-FSH antibody were similar between FE999049 group and GONAL-F group in trial 000145, ESTHER-1 and ESTHER-2 trial. None of the antibodies exhibited neutralizing effects.

The safety profile of FE999049 were compatible with currently available rFSH products. Concerning OHSS, the rate was lower in FE999049 group than in active comparator group.

2.5 Bridging Study Evaluation

Comparison of the PK of FE 999049 after a single dose was based on data from three phase 1 trials: CS01 in Caucasian, CS03 in Japanese (N=24) and Caucasian, and 000152 in Chinese women (N=24), respectively. Comparison of FSH exposure after once daily dosing was based on a population PK model estimated on data from phase 2 trials 000009 in EU and 000124 in Japan, and from phase 3 trials ESTHER-1 in EU/ROW, 000273 in Japan and 000145 in China/PanAsia. In healthy subjects, the FSH concentration profiles were overall similar between Caucasian, Japanese and Chinese subjects. Total exposure (AUC) tended to be 1.1-1.5 fold higher in Chinese subjects as compared to Caucasian and Japanese subjects.

In IVF/ICSI patients, total FSH exposure was similar between East Asian and Caucasian patients, with mean AUCtau estimated to be 349 and 363 h*IU/L, respectively. After correction for differences in dose, East Asian had a 1.17 fold higher exposure compared to Caucasian. This minor difference is explained by the difference in body weight between East Asian and Caucasian subjects. Overall, race is not a sensitive factor on FE 999049 PK.

Efficacy of the REKOVELLE did not show ethnical differences. However, there were ethnical differences in the safety profile, especially the incidence rate of OHSS. The incidence of OHSS was higher in Asian population (trial 000145, 000273) than in Caucasian (ESTHER-1, ESTHER-2), regardless of the rFSH regimen applied. Although there were ethnical differences in safety profile, no significant clinical impact was observed. No further

bridging study was needed.

2.6 Conclusion

This multidisciplinary review recommends approval for REKOVELLE (follitropin delta) for the indication of 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.

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

3. Post-Marketing Requirements

No specific RMP was required.