Post-marketing surveillance (PMS) protocol for

Pergoveris™

Version 2.0, 23 July 2015

PASS Information

Title	*Post-marketing surveillance (PMS) for Pergoveris™ in women with severe deficiency of Luteinizing Hormone(LH) and Follicle-Stimulating Hormone(FSH) defined by less than 1.2 IU/L of endogenous serum LH*
Study protocol number	*EMR 200061-507*
Protocol version identifier	*Version 2.0*
Date of last version of protocol	*23 July 2015*
EU PAS register number	*NA*
Active substance	*Follitropin alfa 150IU is mixed with Lutropin alfa 75IU*
Medicinal product	*Pergoveris*
Product reference	*NA*
Procedure number	*Biopharmaceutical Quality Management Division-454 (2014.11.11)*
Marketing authorisation holder(s)	*Merck Ltd. Korea*
Joint PASS	*No*
Research question and objectives	*To analyze safety and efficacy information on Pergoveris™ in post-marketing uses, as well as factors likely to influence safety and efficacy.* *Primary objective: To get safety information in patients using Pergoveris™* *Primary endpoint:* *Evaluation of frequency and severity of Adverse Event(AE) to occur following administration of PergoverisTM* *Secondary endpoints:* *① Percentage of patients with at least one follicle in more than 17mm of diameter on ultrasonography* *② Clinical pregnancy rate* *Data Analysis:* *Comparative analysis on effective ratio by factor and incidence rate of AE by factor using proper statistical methods such as Chi-square test, Fisher's exact test, Logistic regression, and t-test in Package SAS with descriptive analysis method*

Country(-ies) of study	*Korea, approximately 16 sites,* *a total of 600 or more capable of final evaluation during the study period by May 10th of 2017 from the product approval date.*
Author	PPD , *Merck Ltd. Korea*

Marketing authorisation holder(s)

Marketing authorisation holder(s)	*Merck Ltd. Korea*
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Abbreviation and Definitions

Abbreviations and Terms	Full name in English	Full name in Korean
FSH	Follicle-Stimulating Hormone	난포자극 호르몬
LH	Luteinizing Hormone	황체형성 호르몬
hCG	Human Chorionic Gonadotropin	인융모생식샘자극호르몬
r-hFSH	Recombinant Human Follicle-Stimulating Hormone	재조합 인난포자극호르몬
r-hLH	Recombinant Human Luteinizing Hormone	재조합 인황체형성호르몬
PCOD	Polycystic Ovary Disease	다낭성 난소질환
OHSS	Ovarian Hyperstimulation Syndrome	난소과자극증후군
hMG	Human Menopausal Gonadotropin	사람폐경생식샘자극호르몬
IVF	*in vitro* fertilization	체외수정
ART	Assisted reproductive technology	보조생식기술
Hypogonadotropic Hypogonadism	Hypogonadotropic hypogonadism	저생식샘자극호르몬생식샘저하증
IUI	Intrauterine Insemination	자궁 내 인공수정
OI	Ovulation Induction	배란 유도
IVF-ET	In Vitro Fertilization - Embryo Transfer	체외인공수정
GIFT	Gamete Intra-Fallopian Transfer	생식세포 난관 내 이식술
ZIFT	Zygote Intra-Fallopian Transfer	접합자 난관 내 이식술
ICSI	Intra Cytoplasmic Sperm Injection	세포질 내 정자 주입법
MCD	Menstrual Cycle Day	월경주기날짜
PO	By mouth (per os)	경구투여
IV	Intravenous	정맥주사
IM	Intramuscular	근육주사
SC	Subcutaneous	피하주사
SL	Sublingual	설하투여
TD	Transdermal	경피의 (피부에 부착)

I. Information on Safety

1 Problems at the Stage of Development

'Pergoveris™' is combination that Follitropin alfa 150IU is mixed with Lutropin alfa 75IU, which was developed for the purpose of stimulating follicle development in female patients with severe deficiency in LH and FSH defined by less than 1.21U/L of endogenous serum LH.
Follitropin alfa, one of active ingredients of Pergoveris™, has been used worldwide in order to induce follicle development in infertile patients for past dozens of years. However, it was demonstrated that single treatment of r-hFSH in patients severely deficient in FSH and LH could not maintain a proper LH level in the body, and combination with r-hLH was effective in follicle development stimulation.

When Merck Ltd. firstly developed r-hLH product, Ruberis Inj.(Lutropin alfa), Merck conducted phase 2, 3 trials to evaluate safety and efficacy following concurrent administration of r-hFSH products, Follitropin alfa and Lutropin alfa, in women with severe deficiency in LH and FSH. These trials are applicable to Pergoveris™ for following grounds:

- Follitropin alfa and Lutropin alfa are gene-recombinant gonadotropin, and actually FSH and LH are secreted and circulated together during the human menstruation cycle.
- 'Pergoveris™' has the same active ingredients as Merck's Gonal-F Inj. (Follitropin alfa) and Ruberis Inj.(Lutropin alfa) which were already approved for same patients and are being marketed.
- Two bioavailability studies(IMP 23722, IMP 23718) proved bioequivalence, where comparison was made between the combined treatment of Follitropin alfa and Lutropin alfa mixed at a fixed ratio and the administration of Follitropin alfa or Lutropin alfa. Also, combination of Follitropin alfa and Lutropin alfa was safe and had good tolerability.
- 'Women with severe deficiency in LH and FSH defined by less than 1.2 IU/L of endogenous serum LH', subjects of administration of Pergoveris™, are rare disease patients with a very low prevalence, so it is difficult to perform additional clinical trials targeted at same patients.

1.1. Phase 1 trial (GF6137)

This study was a phase 1 trial with the aim of evaluating the pharmacokinetics of r-hLH and the pharmacokinetic and pharmacodynamics interaction of r-hLH and r-hFSH, where the pituitary function of 12 healthy adult women was down-regulated. As a result, no pharmacokinetic interaction between r-hLH and r-hFSH and clinically related manufacturing interaction were found, and when r-hLH and r-hFSH were combined or each of them was subcutaneously injected one time, those 12 healthy women showed good

tolerability. AEs were burning sensation and headache, which may occur commonly, and it was though that such AEs were caused by a lowered estrogen level from the down-regulated pituitary function, CCI

1.2. Phase 1 trial (IMP 23718, IMP 23722)

IMP 23718 and IMP 23722 studies were phase 1 trials, which intended to evaluate the relative bioavailability and bioequivalence of FSH or LH after r-hFSH(IMP23718) or r-hLH(IMP 23722) was subcutaneously injected one time or Pergoveris™ was subcutaneously injected one time to healthy female subjects with down-regulated pituitary function, as well as tolerability and AEs when r-hFSH/r-hLH were administered at a fixed rate . In the IMP 23718 study, CCI cases of AEs were reported in 36 subjects, and in the IMP 23722 study, CCI cases of AEs were reported in 81 subjects.

Among CCI cases of AEs found in the IMP23718 study, CCI A commonly reported AE from comparator and study drug was headache, no SAEs were reported, and there were no AE-induced dropouts. CCI

Among CCI cases of AEs found in the IMP 23722 study, CCI A commonly reported AE during the trial period was headache, and no severe or serious AEs were reported.

The said AEs are suggested in detail in the table below.[1)]

CCI

[redacted]

1.3. Phase 2/3 trial (GF6253)

This study was a phase 2/3 trial where 10 institutions participated in Europe and Israel in order to evaluate safety of r-hLH supportive of r-hFSH therapy used to induce follicle development in women deficient in FSH or LH with anovulation. To decide a minimum effective dose, a dose of r-hFSH was fixed to 150 IU/day, doses of r-hLH were set as 0, 25, 75, 225 IU/day, and they were administered up to 3 cycles(20 days per cycle) in order to evaluate safety and efficacy.

[redacted]. Most commonly reported AEs included headache, pelvic pain, abdominal pain, breast pain, nausea, drowsiness, and ovary abnormality, and these AEs were similar to those reported when only r-hFSH was administered. Most of AEs were mild(79%) to moderate(19%), and two cases of each one of shock after a traffic accident

[redacted]

[redacted]

CCI

[redacted]

[redacted]

1.4. Phase 2/ 3 trial (GF6905)

This study was a phase 2/3 trial where a total of 14 institutions participated in the U.S. to evaluate the safety of r-hLH supportive of r-hFSH therapy and decide its minimum effective dose in order to induce follicle development in women having hypogonadotropic hypogonadism with anovulation. In this trial, similarly to the GF6253 trial, a dose of r-hFSH was fixed to 150 IU/day, and doses of r-hLH were set to 0, 25, 75, and 225 IU/day, and their safety and efficacy were evaluated by administering them up to 3 cycles(21 days per cycle). [redacted]. Most of commonly reported AEs included headache, pelvic pain, ovarian cyst, abdominal pain, breast pain, menstrual pain, and nausea. Severity of all AEs were mostly mild (62%) to moderate(35%), no SAEs were reported, and no patients discontinued the trial due to AE.[1)] The said AEs are suggested in detail in the table below.

[redacted]

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1.5. Phase 3 trial and PMS

Some studies reported that just r-hFSH administration was enough without addition of r-hLH for follicle ripening, but according to other studies, addition of r-hLH is necessary in order to maintain a blood estrogen level at a proper level and develop the endometrium in some patients. However, when external fertilization is conducted in an infertile patient secreting normal gonadotropin, combination of r-hFSH and r-hLH for controlled ovarian stimulation is still controversial.[3)]

Combination therapy of r-hFSH and r-hLH after artificial inhibition of LH generation was not effective in patients aged less than 35 years but was highly effective in those aged more than 35 years. Also, several researchers explained that due to low reactivity to r-hFSH, addition of r-hLH was important in follicle ripening and estradiol generation in patients who received a very high dose of r-hFSH.[4)5)]

With regard to safety, other than AEs found during use of r-hFSH, no SAEs appeared. Temporary redness was found on the injection site but it appeared similarly to r-hFSH or r-hLH administration, so it was not thought to be clinically significant.

Also, in the PMS on Ruberis Inj.(r-hLH), r-hLH was not effective in young infertile patients having a normal gonadotropin level. The effect of r-hLH could hardly be defined because few studies have been made in a specific patient population well responding to the combination of r-hFSH and r-hLH, and there are few available data, but the effect of r-hLH was shown to be high in infertile women aged more than 35 years with deficiency in LH.

The safety of Pergoveris™ can also be demonstrated through post-marketing uses of Merck's Gonal-F/Pen Inj.(r-hFSH) and Ruberis Inj. (r-hLH), which were used using the same active ingredient. Gonal-F/Pen Since

Inj.(r-hFSH) and Ruberis Inj. (r-hLH) were firstly marketed in Europe in 1995 and 2000, respectively, they have been used for reproductive care worldwide, and no safety-related SAEs have been reported.[6)]

1.6. Conclusion on benefit/risk of Pergoveris

The indication for Pergoveris™, 'Severe deficiency in LH and FSH defined by less than 1.2 IU/L of endogenous serum LH', is a reproductive rare disease characterized by amenorrhea, hypoestrogenism, and a low serum gonadotropin level. Merck Ltd. suggested the role of r-hLH in follicle development induced by r-hFSH in patients with these diseases through clinical trials, as well as systematic consideration of its safety and efficacy.

Upon concurrent administration of FSH and LH to patients with severe deficiency in FSH and LH, clinically significant outcomes occurred such as follicle growth, increased estradiol, and increased serum progesterone level. Also, a clinical trial(GF6253), which intended to identify a minimum effective dose of r-hLH supportive of the induction of follicle development of r-hFSHupon concurrent administration of r-hFSH/r-hLH, revealed that a minimum effective dose of r-hLH to r-hFSH 150IU was 75IU.

As a result of investigating the safety of Pergoveris™ in a clinical trial with each ingredient of r-hFSH and r-hLH, both of them had good tolerance. Two cases of AEs of abortion and traffic accident occurred, and no patients had antibody to Pergoveris. Also, safety of Pergoveris could be demonstrated through post-marketing safety-related information of Gonal-F Inj. (r-hFSH) and Ruberis Inj. (r-hLH) containing the same ingredient as Pergoveris™, as well.

Pergoveris™ enables concurrent administration of two ingredients of r-hFSH and r-hLH in a vial to patients, so it is expected that the dosing frequency will decrease, and problems will be improved such as potential error during dilution through convenient administration procedure and low compliance of the patient, compared with two-time administration of each ingredient.

Seen from the above-mentioned reasons, the benefit of Pergoveris™ will overweigh the risk.

2 Problems of Similar Products

2.1. Follitropin alpha (Gonal-F Inj.)

1) Undesirable ovarian hyperstimulation was observed, so a possibility of ovarian hyperstimulation shall be carefully observed during the whole treatment process.
2) Upon intramuscular injection or subcutaneous injection, bruise, pain, redness, swelling and itching may appear on the injection site, and most of them are not serious. No systemic reactions were

observed.

3) Risk of extrauterine pregnancy and plural pregnancy a little increased.

4) Rarely, arterial thromboembolism associated with menotrophin/hCG administration occurred. This event may appear upon Gonal-F/hCG therapy, tool.

2.2. Lutropin alpha (Ruberis Inj.)

1) Pergoveris is concurrently administered with Follitropin alfa to stimulate follicle development, so it is difficult to see what ingredient caused a side effect. There have been many urine-derived drug uses including hLH, and it will be very similar to urine-derived hLH except safety, hypersensitivity, and injection site reaction of Pergoveris.

2) Application site: In a clinical trial, mild to moderate injection site reactions(bruise, pain, redness, pruritus, swelling) of Lutropin alpha and Pergoveris were found to be 7.4% and 0.9%, respectively, and no severe injection site reactions were reported. No systemic allergic reactions were reported, too.

3) Reproductive system: OHSS was observed in less than 6% of patients treated with Pergoveris, and no severe OHSS was reported. In addition, ovary cyst, breast pain, and extrauterine pregnancy may occur. Particularly, there is a higher probability of extrauterine pregnancy in women with history of fallopian tube disease.

4) General abnormalities: Headache and drowsiness were reported.

5) Gastrointestinal disorders: Nausea, abdominal pain, and pelvic pain appeared.

6) Regarding menotrophin(hMG) administration, rarely, thromboembolism, twisted appendages(complication of ovarian enlargement), intraperitoneal haemorrhage occurred. These events were not observed when Pergoveris was administered, but there is a possibility of occurrence.

3 Problems Considered from Uses in Countries

3.1. DO NOT ADMINISTER TO FOLLOWING PATIENTS

1) Patients with hypersensitivity to Follitropin alfa or Lutropin alfa, or other ingredient of Pergoveris
2) Patients with pituitary or hypothalamus tumor
3) Patients with enlarged ovary or ovarian cyst irrespective of polycystic ovary syndrome(PCOD)
4) Patients with gynecological hemorrhage of unknown cause
5) Patients with ovarian cancer or uterine cancer, or breast cancer
6) Patients with primary ovarian failure
7) Patients with transformed reproductive organ disabling pregnancy
8) Patients with fibroid tumors disabling pregnancy
9) Pregnant women and nursing women

3.2. CAREFULLY ADMINISTER TO FOLLOWING PATIENTS

When Pergoveris is administered to patients with porphyria or family history of porphyria, careful monitoring is necessary. When such symptom is worsened or initially appears, treatment is required to be discontinued.

3.3. Adverse event(AE)

AEs observed from uses in countries are as follows:

1) Very common (≥1/10)

① Ovarian cyst
② Headache

2) Common (≥1/100, < 1/10)

① Abdominal pain, pelvic pain, breast pain
② Nausea, vomiting, diarrhea, abdominal cramps, abdominal distension
③ Drowsiness
④ Injection site reactions(pain, redness, itching, bruise, swelling, etc.)

3) Uncommon (≥1/1,000, < 1/100)

① Ovarian Hyperstimulation Syndrome(OHSS)

: OHSS is different from simple ovarian enlargement. OHSS is characterized by increased severity, significant ovarian enlargement, high blood sex steroid level, and increased vascular permeability, and particularly, increased vascular permeability may lead to accumulated fluids in the peritoneum and pleura, and rarely, pericardial cavity. In case of severe OHSS, gastrointestinal symptoms may occur such as abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, hypouresis, nausea, vomiting, and diarrhea, and clinical evaluation can be conducted with decreased blood, hemoconcentration, electrolyte imbalance, ascites, intraperitoneal hemorrhage, pleural effusion, hydrothorax, acute respiratory failure, and thromboembolism. Also, severe OHSS may be accompanied by pulmonary embolism, ischemic stroke, and myocardial infarction, very rarely.

Generally, OHSS gets naturally resolved with the beginning of menstruation. When severe OHSS occurs and continues, gonadotropin treatment shall be discontinued, and the patient shall be hospitalized to start receiving special treatment for OHSS. OHSS occurs at higher frequency in patients with polycystic ovarian disease.

4) Rare (≥1/10,000, < 1/1,000)

① Thromboembolism

5) Very rare (<1/10,000)

① Systemic allergic reaction(mild erythema, redness, facial swelling, urticaria, edema, dyspnoea). Severe allergic reaction cases were also reported, including anaphylactic reaction.

② Worsened asthma

3.4. Precautions

1) Pergoveris contains material having a strong gonadotropic effect likely to cause mild-severe adverse reactions, so it shall be prescribed by the physician specializing in reproductive care.
2) Gonadotropin treatment shall be conducted by a medical specialist who holds proper monitoring facilities and specializes in the use of Pergoveris. For safe and efficient use of Pergoveris, ovarian reaction shall be routinely monitored by ultrasonography or together with serum estradiol level test. Reaction to FSH/LH administration may differ by patient, and no reaction may occur in some patients.
3) Pergoveris shall only be administered by a person who is voluntary and has received training about the administration method, and the patient shall take advice of a medical specialist. The first injection shall be done under direct medical supervision.
4) Pergoveris contains less than 1mmol (23mg) of sodium per vial, that is, it is essentially sodium free. Pergoveris contains 30mg white sugar, so this point shall be considered when it is administered to diabetic patients.
5) Before starting treatment, proper evaluation on infertility of each of a couple shall be performed, and whether there are contraindications estimated for pregnancy shall be checked. Particularly, patients diagnosed with hypothyroidism, adrenocortical insufficiency, hyperprolactinemia, and pituitary or hypothalamus tumor shall receive proper and special treatment.
6) Patients taking follicle stimulation have an increased risk of incurring hyperstimulation such as estrogen over-reaction and development of multiple follicles.
7) Concurrent administration of Follitropin alfa and Lutropin alfa 75IU in clinical trials increased the reactivity of ovary to gonadotropin. If a dose of FSH is required to be increased, it is desirable to increase a dose of Follitropin alfa by 37.5-75 IU at an interval of 7-14 days.
8) Plural pregnancy: Incidence rate of plural pregnancy increases rather in ovulation inducing treatment than spontaneous pregnancy. Most of plural pregnancies were twins. To minimize risk of plural pregnancy, careful observation of ovarian reaction is required, and potential risk of plural pregnancy shall be informed to the patient before starting treatment.
9) Abortion: An abortion rate is higher in patients using Pergoveris than healthy population.
10) Extrauterine pregnancy: If a woman with history of oviduct disease becomes pregnant by spontaneous pregnancy or reproductive care, there is risk of extrauterine pregnancy. The incidence rate of extrauterine pregnancy following *in vitro* fertilization(IVF) was reported as 2~5%, while that in

healthy population was reported as 1~1.5%.

11) Genital tumor: Ovarian tumor and other genital tumor(benign and malignant) were reported in women who received combination therapy for reproductive care. Whether gonadotropin treatment increases such tumor risk in infertile women has not been established, yet.

12) Congenital malformation: Post-ART(assisted reproductive technology) incidence of malformation is a little higher than spontaneous pregnancy. It is thought that this is caused by difference in parents' characteristics(e.g. mother's age, characteristic of sperm) and plural pregnancy.

13) Pulmonary and vascular complications: Generally, a woman having risk factor of thromboembolism such as personal medical history or family history may have an increased risk from gonadotropin treatment. In such a woman, the benefit of gonadotropin administration shall overweigh the risk. However, it increases the risk of pregnancy itself or thromboembolism.

14) Studies on driving ability and mechanical operation with Pergoveris have not been made, yet.

3.5. Interaction

This drug shall not be mixed with any drug other than Follitropin alfa for administration.

3.6. Use in pregnancy and lactation

This drug shall not be administered to pregnant women and nursing women.

3.7. Overdosing

Influence by overdosing of Pergoveris is not known, but there is a possibility of OHSS.

3.8. Cautions at use

1) Pergoveris is disposable subcutaneous injection, and when it is dissolved with accompanying solvent, it contains Follitropin alfa 150IU and Lutropin alfa 75IU per 1 mL.

2) Pergoveris shall be dissolved in solvent immediately before use, and when the dissolved solution contains particles or is not clear, it shall not be injected.

3) When administration of Pergoveris is missed, a doubled dose shall not be administered to regain the missed dose. A subsequent dose shall not be decided in discussion with the prescribing physician.

4) The storage temperature(25℃ or less) shall be followed, and the vial shall not be taken out of the case and kept as it is in order to block out sunlight.

5) Preparation of administration solution and administration method

① Pre-preparation arrangement: Wash out the hands and put down the following articles kept in a clean state on the clean floor.

- Pergoveris™ vial: 1

- Solvent vial: 1
- Alcohol swab for disinfection: 2
- Syringe: 1
- Needle for preparation and fine needle for subcutaneous injection: each 1

② Remove the protective cap of the solvent vial. Put the needle for preparation in a new disposable syringe and pull the plunger to the approximately 1mL mark point. Put the syringe into the vial as it is, push the push stick to discharge the air, and slowly take out the whole solvent by upending the vial. Put down the syringe on the floor slowly while paying attention not to contact the needle.

③ Remove the protective cap of the Pergoveris™ vial, pick up the syringe containing solvent, and slowly inject the solvent into the vial. Softly turn without taking out the syringe. Do not shake the solution. After powder is dissolved(usually it is directly dissolved), make sure that the solution is clear and there are no particles. Taking out the solution within the syringe by upending the vial.

④ Change and insert the needle for preparation into the fine needle for subcutaneous injection. If air bubbles are observed within the syringe, grasp the syringe for the needle side up, and softly tap the syringe until air bubbles will gather toward the top. Push the push stick so that air bubbles can be pushed out.

⑤ Among body parts(e.g. abdomen, front of the thigh, etc.) previously informed by the physician or nurse, select the injection site and rub with alcohol swab. Grasp the skin on the injection site and subcutaneously insert the needle by puncturing at 45~90 degrees as if throwing darts. Do not perform direct intravenous injection. Softly push the plunger and slowly inject the whole solution. After end of injection, take out the needle and rub round with alcohol swab on the injection site.

⑥ Discard: After end of injection, immediately discard the used needle, syringe, empty glass container, etc. in a safe manner. Discard any remaining liquid, certainly.

II. PMS Plan and Special Investigation Plan

1 Objective of PMS

To analyze safety and efficacy information on Pergoveris™ in post-marketing uses, as well as factors likely to influence safety and efficacy.

Primary objective: To get safety information in patients using Pergoveris™

1) Serious Adverse Event(SAE)/Adverse Drug Reaction(ADR)
   ① If causing death or threatening one's life
   ② If hospitalization or prolonged duration of hospitalization is necessary
   ③ If causing continuous or significant disability or dysfunction
   ④ If causing congenital malformation or abnormality
   ⑤ Other medically critical conditions
2) AE/ADR not expected in Precautions
   (hereafter referred to as "Unexpected ADR")
3) Already known ADR
4) Non-serious Adverse Drug Reaction
5) Other safety/efficacy related information(influence upon clinical laboratory value, etc.)

2 Patient Population

Women with severe deficiency of Luteinizing Hormone(LH) and Follicle-Stimulating Hormone(FSH) defined by less than 1.2 IU/L of endogenous serum LH

3 Sample Size

A total of 600 cases or more shall be collected as per the number of report cases pursuant to the Paragraph 3 of Article 6 of the "Re-examination Standards for New Drugs Etc." (Ministry of Food and Drug Safety Notification No. 2014-61) and the number of cases within additional surveillance period according to the direction pursuant to the Article 69 of the "Pharmaceutical Affairs Law".

4 Planned Investigation Period

An investigation period for 4 years has been finished from February 22, 2010 to February 21, 2014, however, the required number of cases will be collected within the additional study period (by May 10, 2017) pursuant to the Article 69 of the "Pharmaceutical Affairs Law" and the surveillance report (including the re-examination report) shall be submitted by August 10, 2017.

5 Planned Institution

This PMS is executed at approximately 10 centers including hospital affiliated with university, department of obstetrics & gynecology and center for reproductive care at general hospital, and obstetrics & gynecology clinic.

6 Items and Method of PMS

6.1. Items of PMS

6.1.1 Information of institution

Institution name, department name, and investigator name shall be written in the first page of CRF.

1) Institution name: Write the (medical) institution name.
2) Department name: Write the department name.
3) Investigator name: Write the name of the investigator who concluded the agreement and write his/her signature.

6.1.2 Basic information of subject

Initial and date of birth of the patient shall be written in the 'Patient background' field of the CRF.

1) Patient initial: Write the English initial of the last name of the patient.
2) Date of birth: Write the patient's date of birth in order of day(two digits)/month(two digits)/year(four digits).

6.1.3 Medical history of subject

Whether there is concurrent disease, whether there is allergic history, period and cause for infertility, whether ART(Assisted Reproduction Techniques) was used previously, and if ART was used, the ART procedure used shall be investigated.

1) Concurrent disease: Separately indicate any patient with hepatic impairment or renal impairment among concurrent diseases, and directly write other concurrent disease.
2) Allergic history: Tick in 'Yes' or 'No', and if tick in 'Yes', write the details.
3) Period for infertility: Write a period from the date when infertility was diagnosed to present in the unit of 'month' and 'year'.
4) Causes for infertility:
   ① Ovary factor: ovulatory disorder
   - Tick if the brain is damaged or pituitary hormone secretion is insufficient, or prolactin is increased, or if there is ovulatory disorder such as anovulation or oligoovulation due to ovary disease such as polycystic ovary disease.
   ② Cervical factor

Tick if there is Abnormalities of Sperm-Mucus Interaction or cervicitis, or cervical intraepithelial neoplasia, or related medical treatment, resulting in damage to the uterocervical canal and causing infertility.

③Uterine factor

Tick if congenital malformation of the uterus, myoma of the uterus, endometrial adhesion, endometrial polyp, and chronic endometritis as anatomical factors, leading to infertility.

④Oviduct factor

Tick if oviduct adhesion resulting from a sexually transmitted disease or inflammatory disease in the reproductive organs interferes with sperm-egg binding, leading to infertility.

⑤ Intra-abdominal abnormality

Tick if endometriosis, pelvic inflammatory disease, and pelvic adhesion interfere with the process that an egg ovulated from the ovary enters the oviduct, failing in fertilization.

⑥ Male infertility factor

Tick if infertility is caused by the male such as male sperm abnormality.

⑦ Immunological factor

Tick if semen or sperm acts as antigen and generates antibody in the female's body, resulting in infertility.

⑧ Unknown cause

If the cause is unknown, tick in 'Unknown cause'.

5) Previous ART experience: Tick in 'Yes' or 'No', and if tick in 'Yes', write the number of times.

6) ART* procedure: Tick in one of 'OI/ IUI/ IVF-ET/ GIFT/ ZIFT/ ICSI/ Others', and in case of 'Others', write the details.

- Items of ART* procedure

① OI (Ovulation Induction)

② IUI (Intra Uterine Insemination)

③ IVF-ET (In Vitro Fertilization - Embryo Transfer)

④ GIFT (Gamete Intra-Fallopian Transfer)

⑤ ZIFT (Zygote Intra-Fallopian Transfer)

⑨ ICSI (Intra Cytoplasmic Sperm Injection)

⑩ Others

6.1.4 Indication for Pergoveris™

1) Tick in 'She is a woman with severe deficiency of Luteinizing Hormone(LH) and Follicle-Stimulating Hormone(FSH), which is the indication for Pergoveris™, defined by less than 1.2 IU/L of endogenous serum LH'

2) Write the levels of serum LH and FSH measured within a year before administration of Pergoveris™.

3) Write the measured date of LH and FSH in order of day(two digits)/month(two digits)/year(four digits), and mention day __ from the menstruation start date, as well.
4) In case of amenorrhea, write ND in the 'Day __ from the menstruation start date' field.

6.1.5 Previous treatments for infertility

Before administration of Pergoveris, drug name(product name) administered for treatment of infertility and the administration cycle shall be investigated.
Write any drug which were used for treatment of infertility prior to administration of Pergoveris™, although it is not being currently used.

1) Presence or absence of previous treatment for infertility: Tick in 'Yes' or 'No'.
2) If tick in 'Yes', write the name of drug(product) used and the administration cycle without omission, and if the investigator has other opinion of the drug, state it in the 'Comment' field.

6.1.6 Current Pergoveris uses

Daily dose, administration period(administration start date, end date), and the reason for change of a dose, if any, shall be written.

1) Administration start date and end date: Administration start date and end date shall be written in order of day(two digits)/month(two digits)/year(four digits). In case of end date, last administration date of Pergoveris™ shall be written.
2) Upon an increased FSH dose, if Follitropin alfa is additionally administered, write not in the 'Pergoveris™ dose change' field but in the 'Concomitant medication' field.

6.1.7 Concomitant medication

Name of concomitant medication(product), which is concurrently used during administration of Pergoveris, dose, route of administration, administration period(administration start date, end date), and purpose of administration shall be investigated.

1) Presence or absence of concomitant medication: Tick in 'Yes' or 'No'.
2) If tick in 'Yes', write, name of concomitant medication(product), total daily dose, route of administration, administration period(administration start date, end date), and purpose of administration without omission.
3) Daily dose: Write a total daily dose with unit. The unit shall be mg, but in case of combination which can hardly be indicated in mg, it can be indicated in the unit of capsule or tablet.
4) Route of administration: Check the following routes of administration and write in a number. However, if not applicable to one of followings, write as '8' and the route of administration together.
   (1)PO (Per os)
   (2)IV (Intravenous)
   (3)IM (Intramuscular)

(4)SC (Subcutaneous)

(5)SL (Sublingual)

(6)Ophthalmic

(7)TD, Transdermal

(8)Others

5) Administration period: The administration start date and the administration end date shall be written in order of day(two digits)/month(two digits)/year(four digits), and if the administration is in progress, write as 'ongoing' or 'continue'.

6) Purpose of administration: The purpose(indication) of administration of the concomitant medication shall be written.

6.1.8 Safety

Safety items shall be investigated by medical examination by interview or spontaneous report by the patient whenever the patient visits the hospital, including whether AE(including side effect) occurred during or after administration of Pergoveris™, type, onset date, disappearance date, severity, causal relationship with Pergoveris, measures on administration of Pergoveris, progress, and if SAE occurred.

6.1.9 Efficacy

Whether the number of follicles in more than 17mm of mean diameter on ultrasonography is at least 1(one) shall be checked, and percentage(%) of subjects who are thought to be 'effective' shall be investigated among subjects of efficacy evaluation.

1) HCG administration: Once HCG is administered, tick in 'Yes' and write the administered date. If not, tick in 'No'.

2) Follicular growth: Count the number of follicles in more than 17mm of diameter on ultrasonography, and if it is 1 or more, tick in 'Yes', and if it is 0, tick in 'No'. If the number of follicles in more than 17mm of diameter is 0 but if decision is impossible not by ineffectiveness of the drug but by other parameter , tick in 'Undecidable'.

3) Clinical pregnancy: Perform urine HCG test or ultrasonography to check clinical pregnancy, and tick in each item of the executed examination.

4) Urine HCG test: If urine HCG test is executed, tick in 'Yes', and if not, tick in 'No'. If the examination date is conducted, examination date shall be written in order of day(two digits)/month(two digits)/year(four digits), and if the test result is positive, tick in 'Positive', and if negative, tick in 'Negative'.

5) Ultrasonography: If ultrasonography is executed, tick in 'Yes', and if not, tick in 'No'. If the examination date is conducted, examination date shall be written in order of day(two digits)/month(two digits)/year(four digits), and if pregnancy is not clinically found on

ultrasonography, tick in 'Yes' and mention the gestational age. In case of no clinical pregnancy, tick in 'No'.

6.2. PMS method

6.2.1. General matters

1) Written agreement shall be concluded prior to start of PMS.
2) PMS shall be designed to see current AEs under actual use conditions.
3) PMS shall be conducted by systematically extracting cases in a way of continuous investigation.
4) It is necessary to see the occurrences of AEs directly after Pergoveris is marketed, so PMS plan shall be prepared prior to release, and PMS shall be commenced as early as possible following release.
5) For the purpose of finding out unexpected ADRs, among AEs incurred during or after administration, those that are thought to have no causal relationship with Pergoveris shall be collected.
6) Even in case of dropout, whether or not AE occurred is found through follow-up, the dropout shall be subject of safety evaluation, and for dropout not followed-up, the reason shall be stated.

6.2.1.1. Intensive check points of PMS

Any notable problem has not been found at the stage of development, and there is no matter required to be intensively investigated. Accordingly, during the PMS period, data of unexpected AEs will be collected, and if any problem of efficacy and safety occurs compared to pre-marketing, onset of AE and causal relationship with Pergoveris are to be intensively observed and investigated.

6.2.1.2. Request for PMS

For execution of PMS, medical institutions and medical staff capable of fully achieving the objective of PMS shall be selected, PMS shall be requested in writing, Merck's PMS agreement form or institution's fixed form shall be filled in, and both the institution and Merck shall keep each 1(one) copy. During the PMS period, the subinvestigator shall routinely visit the investigator to check the progress, see if PMS is proceeded in compliance with protocol, and may demand any necessary matters from the investigator.

6.2.1.3. Collection of CRFs

All completely prepared CRFs shall be collected by repeated visit when it goes toward the end of PMS following the PMS start date. When completed CRFs are collected from the investigator, whether there is any omission among the set items of PMS, and the condition is appropriate shall be checked, and if necessary, addition or modification shall be requested.

6.2.1.4. Request for reinvestigation

Whether items are properly entered in collected CRFs shall be checked, and if there is an item omitted in entry, this shall be added/modified/corrected by the investigator, and if collected cases are required to be reinvestigated, reinvestigation shall be requested in writing.

6.2.2. Matters of safety

General incidence rates of AEs and related factors shall be analysed, incidence rates by type of AE, incidence rates of unexpected AEs and serious AEs, severity, outcome, and their relationship with Pergoveris shall be evaluated, and criteria for causal relationship are as mentioned below.

6.2.2.1. Check of seriousness of AE

1) Serious
   ① If causing death or threatening one's life
   ② If hospitalization or prolonged duration of hospitalization is necessary
   ③ If causing continuous or significant disability or dysfunction
   ④ If causing congenital malformation or abnormality
   ⑤ If a medically significant event occurs(It is defined as a medical event, which does not immediately threatens one's life or results in death or hospitalization, but based on proper medical and scientific judgment, may jeopardize the patient and demand intervention [e.g. internal or surgical intervention] to prevent one of other serious outcomes enumerated in the above definitions. Examples of this AE include but not limited to intensive treatment at ER or home for allergic bronchial spasm; blood disease or spasm not leading to hospitalization.)
2) Non-serious

6.2.2.2. Causal relationship decision criteria

1) Certain

- If the context with administration or use of Pergoveris is appropriate, the AE cannot be explained with other drug or chemical substance, or accompanying disease, and upon dechallenge of Pergoveris, a clinically proper reaction appears, and upon rechallenge of Pergoveris as needed, it is decisive in a pharmacological or phenomenological aspect

2) Probable/likely

- If time relationship with administration or use of Pergoveris is reasonable, it is thought that the AE is caused by other drug or chemical substance, or accompanying disease, and upon dechallenge of Pergoveris, a clinically proper reaction appears (no information about rechallenge)

3) Possible

- If time relationship with administration or use of Pergoveris is reasonable but the AE can be explained with other drug or chemical substance, or accompanying disease, and information about dechallenge of Pergoveris is insufficient or unclear

4) Unlikely

- If the AE is a temporary case unlikely to have causal relationship with administration or use of Pergoveris, and it may be appropriately explained that the AE is caused by other drug or chemical substance, or underlying disease

5) Unassessible

- If it is impossible to make a decision due to insufficient or conflicting information, and this neither be supplemented nor identified

6.2.2.3. AE severity decision criteria

1) Mild

- A subjective or objective symptom occurs but this does not make trouble to daily life; if continuous treatment is possible without changing a dose of the drug

2) Moderate

- A symptom to an extent that they negatively affect daily life; a degree requiring reduction or treatment of a dose due to AE

3) Severe

- A symptom to an extent that makes the patients live their routine life well; If the drug is required to be dechallenged due to a severe AE

6.2.2.4. Measures on administration of Pergoveris

1) Do not take any measures.
2) Change of doses
3) Temporary dechallenge
4) Permanent dechallenge

6.2.2.5. Progress

1) Recovered
2) Unchanged

3) Worsened
4) Recovered with sequelae
5) Unknown

6.2.3. Matters of efficacy

1) If there is at least one follicle in more than 17mm of mean diameter on ultrasonography shall be checked, and percentage(%) of patients who are thought to be "effective" shall be investigated among those subject to efficacy evaluation.
   ① Valid: More than one follicle in more than 17mm of diameter on ultrasonography
   ② Invalid: No follicle in more than 17mm of diameter on ultrasonography
   ③ Undecidable: No follicle in more than 17mm of diameter on ultrasonography; it does not result from ineffectiveness of the drug but it is undecidable owing to other parameter
2) Clinical pregnancy rate: Those who are clinically pregnant shall be investigated, and percentage(%) of those pregnant subject to efficacy evaluation shall be investigated.

6.2.4. Matters of selection of subject

Among patients who visited the hospital from the date when each hospital(or clinic) accepted a PMS request and started investigation until the requested sample size would be met, patients who received Pergoveris™ shall be successively entered in the CRFs, and followed up without omission to prevent an omission at reporting, if possible(successive investigation). Also, even if the drug is not initially administered following the opening date of investigation, the drug may be registered, and once the drug is administered although it is not administered initially, it may be registered.

7 Items and Method of Evaluation, and Analysis Method

7.1. Items of evaluation

7.1.1 Composition of subjects

Descriptive analysis shall be conducted on the number of cases requested for PMS, the number of cases with CRFs collected, the number of cases subject to safety evaluation, the number of cases subject to efficacy evaluation, and the number of dropout cases and the reason.

1) Subject of safety evaluation: Those who have been administered Pergoveris™ for once and followed up, safety evaluation shall be conducted.
2) Subject of efficacy evaluation: Among those subject to safety evaluation, patients with follicle size evaluated following administration of Pergoveris™ shall undergo efficacy evaluation.

7.1.2 Items of safety

7.1.2.1 Current AEs onset status

AEs, ADRs, incidence rates of unexpected AEs and serious AEs shall be evaluated in subjects who have been administered Pergoveris^{TM} for once and followed up, general incidence rates of AEs shall be investigated, and a list of onset status of serious AEs, ADRs, or unexpected ADRs by type shall be prepared.

7.1.2.2 Factors likely to influence safety

To look into factors, which are thought to influence safety, a list of AEs onset status by background factor of subjects(demographic factor, therapeutic factor, etc.) shall be completed, and among AEs that are thought to be unrelated with Pergoveris, if there is a specific trend, a list of items for reviewing causal relationship with Pergoveris shall be prepared.

7.1.3 Items of efficacy

In subjects evaluated following administration of Pergoveris, whether there is one or more follicle in 17mm of diameter, clinical pregnancy rate shall be comprehensively judged, and a general effective ratio shall be obtained compared with before treatment. Also, in consideration of factors likely to influence efficacy, if needed, an efficacy list by background factor of subjects(demographic factors, therapeutic factors) shall be completed.

7.2. Evaluation Method and Analysis Method

7.2.1 Evaluation method

Incidence rates of each AE incurred, ADRs, unexpected AEs and serious AEs shall be stated, and general incidence rate of AEs and 95% confidence interval shall be mentioned. Incidence rates of AEs by factor shall be compared, and analysis on relation of occurrence of AEs by factor shall be conducted using statistical method such as Fisher's exact test, Chi-square test, and Logistic regression.
In efficacy evaluation, final evaluation shall be summarized, univariate and multivariate factor analyses shall be carried out on relation with effective ratio by factor using statistical method such as Fisher's exact test, Chi-square test, and Logistic regression.

7.2.2 Analysis method

Based on results obtained from PMS, medical and pharmaceutical decision shall be decided, and statistical analysis shall be conducted on efficacy and safety endpoints.

8 Other Requirements

8.1. Revision of PMS plan

Whether PMS plan is required to be revised shall be examined based on new knowledge obtained while PMS is progressed, and it shall be revised if necessary. Also, even in the case that partial amendment approval was obtained for administration, dosage, or indication during the re-examination period of Pergoveris, whether PMS plan is needed to be revised shall be examined, and it shall be revised if needed.

8.2. Measures upon problem or doubt

If onset of serious unexpected AE is implied, or if a sharp increase in frequency of AE is shown, or if a problem about efficacy and safety is found compared to before marketing, a hypothesis shall be formed and special shall be considered to verify the hypothesis.

8.3. How to report AE

1) All AEs incurred during administration of Pergoveris shall be written in the relevant page of CRF.
2) Upon onset of a SAE, the investigator shall prepare the Merck SAE form and send it to Global Drug Safety (GDS).
   <Global Drug Safety>
   Fax: +49 6151 726914
   E-mail: globaldrugsafety@merckgroup.com
3) If contagion of an infectious matter (e.g. pathogenic or non-pathogenic organism, viral or infectious small particle) through Pergoveris is suspected, this shall be reported as SAE.
4) Although overdosing and carcinogenesis are not always critical as defined in relevant regulations, these events shall be reported in a SAE form and rapidly delivered to GDS.

IV. Reference

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