EU Risk Management Plan

Active substance(s) (INN or common name):	**Follitropin alfa/Lutropin alfa**
Name of Marketing Authorization Holder or Applicant:	**Merck Europe B.V.** **Gustav Mahlerplein 102** **Ito Toren** **1082 MA** **Amsterdam** **Netherlands** **Tel. +31 (0) 207 235 230** **Fax +31 (0) 207 235 239** **e-mail: GlobalDrugSafety@merckgroup.com**

RMP version to be assessed as part of this application:

RMP version number:	6.0
Data Lock Point for this RMP:	30 April 2019
Date of final sign-off:	Document signed electronically, see date of eSignature at the end of the document
Rationale for submitting an updated RMP:	RMP update as per GVP Module V, rev 2.0.1 template.
Summary of significant changes in this RMP:	• The important identified risks of "Ovarian Hyperstimulation Syndrome (OHSS)", "Thromboembolic events, usually with OHSS" and "Hypersensitivity reactions" have been removed. • The important potential risks of "Breast cancer", "Ovarian cancer", Endometrial cancer", "Congenital anomalies" and "Malignant melanoma" have been removed. • The missing information of "Premenopausal women with severe LH and FSH deficiency older than 42 years" has been removed.
Other RMP versions under evaluation:	Not applicable

RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	5.2
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Signatures

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Qualified Person responsible for Pharmacovigilance in the European Economic Area (EEA QPPV)

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Marketing Authorization Holder´s QPPV. The electronic signature is available on file.

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List of Abbreviations

ACTH	Adrenocorticotropic Hormone
ADR	Adverse Drug Reaction
AEs	Adverse Events
ARISg	Adverse Reaction Information System Global
ART	Assisted Reproductive Technology
ASRM	American Society for Reproductive Medicine
ATC	Anatomical Therapeutic Chemical
CHO	Chinese Hamster Ovary
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous System
DLP	Data Lock Point
DNA	Deoxyribonucleic Acid
E2	Estradiol
EEA	European Economic Area
ESHRE	European Society of Human Reproductive and Embryology
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPO	Erythropoietin
EU	European Union
EUROCAT	European Concerted Action on Congenital Anomalies and Twins
FSH	Follicle Stimulating Hormone
FHA	Functional Hypothalamic Amenorrhea
GLOBOCAN	Global Cancer Incidence, Mortality and Prevalence
GnRH	Gonadotropin-releasing Hormone
GPS	Global Patient Safety
GVP	Good Pharmacovigilance Practice
HA	Hypothalamic Amenorrhea
hCG	Human Chorionic Gonadotrophin
hGH	Human Growth Hormone
HH	Hypogonadotropic Hypogonadism
HIV	Human Immunodeficiency Virus

hMG	Human Menopausal Gonadotropin
HP	Hypopituitarism
ICMART	International Committee Monitoring Assisted Reproductive Technologies
ICSI	Intra Cytoplasmic Sperm Injection
ICSR(s)	Individual Case Safety Report(s)
IHH	Isolated Hypogonadotropic Hypogonadism
i.m.	Intramuscular
INN	International Nonproprietary Name
IOC	International Olympic Committee
IU	International Unit
IU/kg	International Unit per Kilogram
IU/L	International Unit per Liter
i.v.	Intravenous
IVF	In-Vitro Fertilization
KS	Kallmann Syndrome
LH	Luteinizing Hormone
LHCG	Lutropin-Choriogonadotropic Hormone
MA	Marketing Authorization
MAR	Medical Assisted Reproduction
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
NICE	National Institute for Health and Care Excellence
OHSS	Ovarian Hyperstimulation Syndrome
OI	Ovulation Induction
PBRER(s)	Periodic Benefit Risk Evaluation Report(s)
PCOS	Polycystic Ovarian Syndrome
PD	Pharmacodynamics
PK	Pharmacokinetics
PL	Package Leaflet
PMS	Post-Marketing Surveillance
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR(s)	Periodic Safety Update Reports

QPPV	Qualified Person for Pharmacovigilance
QT	QT interval
RCOG	Royal College of Obstetricians and Gynecologists
r-hFSH	Recombinant Human Follicle Stimulating Hormone
r-hLH	Recombinant Human Luteinizing Hormone
RMP	Risk Management Plan
s.c.	Subcutaneous
SmPC	Summary of Product Characteristics
TE	Thromboembolic Event
UK	United Kingdom
WFI	Water For Injection
WHO	World Health Organization

Part I: Product(s) Overview

Product(s) Overview

Active substance(s) (International Nonproprietary Name (INN) or common name)	Follitropin alfa/Lutropin alfa
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical (ATC) Code)	Gonadotropin (G03GA30)
Marketing Authorization Holder	Merck Europe B.V. Gustav Mahlerplein 102 Ito Toren 1082 MA Amsterdam Netherlands Tel. +31 (0) 207 235 230 Fax +31 (0) 207 235 239 e-mail: GlobalDrugSafety@merckgroup.com
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Pergoveris®
Marketing Authorization Procedure	Centralized
Brief description of the product	Chemical class Sex hormones and modulators of the genital system, gonadotropins Follitropin alfa/lutropin alfa (Pergoveris®) is a medicinal product containing recombinant human Follicle Stimulating Hormone (r-hFSH; INN: follitropin alfa) and recombinant human Luteinizing Hormone (r-hLH; INN: lutropin alfa) as active substances.
	Summary of mode of action Follitropin alfa triggers the development of mature Graafian follicles. Luteinizing hormone (LH), during the follicular phase, stimulates ovarian theca cells to secrete androgens, which will be used as the substrate by granulosa cell aromatase enzyme to produce oestradiol, supporting FSH induced follicular development. At mid-cycle, high levels of LH trigger corpus luteum formation and ovulation. After ovulation, LH stimulates progesterone production in the corpus luteum by increasing the conversion of cholesterol to pregnenolone. In the stimulation of follicular development in women deficient in LH and FSH, the primary effect resulting from administration of lutropin alfa is an increase in oestradiol secretion by the follicles, the growth of which is stimulated by FSH. In clinical trials, patients with severe FSH and LH deficiency were defined by an endogenous serum LH level <1.2 IU/L (International Unit per Liter).
	Important information about its composition Follitropin alfa/lutropin alfa (Pergoveris®) is a preparation of recombinant human follicle stimulating hormone (follitropin alfa, r-hFSH) and recombinant human luteinizing hormone (lutropin alfa, r-hLH) produced in Chinese hamster ovary (CHO) cells by recombinant deoxyribonucleic acid (DNA) technology.
Hyperlink to the Product Information	**Module 1.3.1 Product Information**
	Current:

Indication(s) in the European Economic Area (EEA)	Pergoveris® is indicated for the stimulation of follicular development in adult women with severe LH and FSH deficiency.
	Proposed: Not applicable
Dosage in the EEA	Current: Pergoveris® should be given as a course of daily injections. Treatment with Pergoveris® should be initiated under the supervision of a physician experienced in the treatment of fertility problems. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and oestrogen response. A treatment regimen commences with the recommended dose of Pergoveris® containing 150 International Units (IU) r-hFSH/75 IU r-hLH daily. If less than the recommended daily dose is used, the follicular response may be unsatisfactory because the amount of lutropin alfa may be insufficient. If an FSH dose increase is deemed appropriate, dose adaptation should preferably be after 7-14 day intervals and preferably by 37.5-75 IU increments using a licensed follitropin alfa preparation. It may be acceptable to extend the duration of stimulation in any one cycle to up to 5 weeks. When an optimal response is obtained, a single injection of 250 micrograms of recombinant human chorionic gonadotrophin (r-hCG) or 5,000 IU to 10,000 IU hCG should be administered 24-48 hours after the last Pergoveris® injection. If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle.
	Proposed: Not applicable

Pharmaceutical form(s) and strengths	Current:
	• Pergoveris® 150 IU/75 IU powder and solvent for solution for injection;
	  • One vial contains 150 IU (equivalent to 11 micrograms) of follitropin alfa (r-hFSH) and 75 IU (equivalent to 3.0 micrograms) of lutropin alfa (r-hLH). One vial of solvent contains 1 milliliter (mL) of Water for Injection (WFI).
	The powder should be reconstituted immediately prior to use with the solvent provided.
	• Pergoveris® solution for injection in a multi-dose pre-filled pen:
	  • Pergoveris (300 IU +150 IU)/ 0.48 mL solution for injection in a pre-filled pen. Each multi-dose pre-filled pen contains 300 IU (equivalent to 22 micrograms) of r-hFSH and 150 IU (equivalent to 6 micrograms) of r-hLH in 0.48 milliliter (mL) solution.
	  • Pergoveris (450 IU + 225 IU)/0.72 mL solution for injection in pre-filled pen. Each multi-dose pre-filled pen contains 450 IU (equivalent to 33 micrograms) of r-hFSH and 225 IU (equivalent to 9 micrograms) of r-hLH in 0.72 mL solution.
	  • Pergoveris (900 IU + 450 IU)/1.44 mL solution for injection in pre-filled pen. Each multi-dose pre-filled pen contains 900 IU (equivalent to 66 micrograms) of r-hFSH and 450 IU (equivalent to 18 micrograms) of r-hLH in 1.44 mL solution.

	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

Part II: Safety Specification

Part II: Module SI Epidemiology of the Indication(s) and Target Population(s)

Indication:

Pergoveris® (follitropin alfa/lutropin alfa) is recommended for the stimulation of follicular development in adult women with severe LH and FSH deficiency, including in fertility treatment.

Failure of gonadotropin releasing hormone (GnRH) secretion or action, or any disruption of LH and FSH secretion and action, may result in LH/FSH deficiency that impairs ovulation and can cause infertility (Yasmin, 2013; Hayes et al., 2000).

GnRH, produced by the hypothalamus, is a key player in normal puberty and sexual development and function. LH, in synergy with FSH, stimulates follicular growth and ovulation. The primary role of FSH is to stimulate the development and maturation of ovarian follicles, whereas, LH stimulates secretion of sex steroids and plays a role in follicular development and maturation (Casarini et al., 2018; Jonas et al., 2018). These two gonadotropins interact on the target cell surface to modulate intracellular gonadotropin signals through Lutropin-Choriogonadotropic Hormone (LHCG) receptors and FSH receptors in a synergistic mode of action to ensure normal follicular growth, development and maturation during the different phases of folliculogensis (Casarini et al., 2018).

Pulsatile secretion of GnRH from the hypothalamus is required for both the initiation and the maintenance of the reproductive axis in humans. Failure of GnRH secretion or action, or any disruption of LH and FSH secretion, results in severe LH/FSH deficiency that impairs ovulation and follicular development and can cause infertility (Yasmin, 2013; Hayes et al., 2000; Marques et al., 2000).

Women may present LH/FSH deficiency (hypogonadotropic women) in association with hypothalamic amenorrhea (HA), anovulation and possibly small gonads (hypogonadism) (Hayes et al., 2000). The World Health Organization (WHO) classification of anovulation categorizes women presenting with low estrogen and low/normal gonadotropin levels as WHO Group I. This group includes women with hypothalamic amenorrhea, hypogonadotropic hypogonadism (HH) and hypopituitarism (HP). Notably, this classification does not cover all patients with severe LH/FSH deficiency (Yasmin, 2013). More recently International Committee Monitoring Assisted Reproductive Technologies (ICMART) has published The International Glossary on Infertility and Fertility Care (Zegers-Hochschild et al., 2017) in which hypogonadotropic hypogonadism was defined as a gonadal failure associated with reduced gametogenesis and reduced gonadal steroid production due to reduced gonadotropin production or action.

The phenotypic presentations of LH/FSH deficiency varies with age of onset (congenital vs. acquired), severity (complete vs. partial), and duration (reversible/functional vs. irreversible/permanent) (Hayes, 2013; Antoniou-Tsigkos et al., 2018, Physiopathology, Diagnosis, and Treatment of Secondary Female Hypogonadism).

The clinical features of congenital GnRH and/or gonadotropin deficiency are typically first manifested at puberty, a time when there is normally a marked increase in GnRH secretion as described above.

Acquired causes, irreversible/permanent and reversible/functional, of HH include Central Nervous System (CNS) or pituitary tumors, infiltrative diseases, infection, brain/pituitary radiation, pituitary apoplexy, head trauma, treatment with drugs such as glucocorticoids, narcotics, GnRH agonist/antagonist and chemotherapy (Antoniou-Tsigkos et al., 2018, Physiopathology, Diagnosis, and Treatment of Secondary Female Hypogonadism). A further endocrine disorder that may co-exist with HH is hypothyroidism (Yasmin, 2013).

Approximately 10% of women with ovulation disorders have a WHO group I ovulation disorder [National Institute for Health and Care Excellence (NICE, 2004)], with HA, which is characterized by low gonadotrophins levels and estrogen deficiency (NICE, 2004). HA is related to profound impairment of reproductive functions including anovulation and infertility. Women's health in this disorder is disturbed in several aspects including the skeletal system, cardiovascular system, and mental problems. Proper diagnosis and treatment of functional HA are important due to the potential risk of infertility arising from chronic amenorrhea (Meczekalski, 2014).

Etiology of HH is not very well described. However, congenital HH, when it is associated with anosmia, is known as Kallmann's syndrome (KS), where the main cause of GnRH insufficiency is the failure of migration of the GnRH secretory neurons to the forebrain (Karges, 2005).

Isolated hypogonadotropic hypogonadism (IHH) usually results from GnRH deficiency, with absence of any other abnormalities. Serum concentrations for LH, FSH, and sex steroids are inappropriately low. Clinical signs and symptoms of hypogonadism include bilateral cryptorchidism in males, absent or incomplete puberty with amenorrhea in females, and infertility. KS accounts for 50–52% of cases with IHH (Beate, 2012).

Congenital HP is uncommon and as with all causes of infertility, must be appropriately investigated before ovulation induction (OI) is considered (NICE, 2004). HP refers to a decreased secretion of pituitary hormones and can result from pituitary tumors or their treatment (Yasmin, 2013). Hypothyroidism can coexist with HH.

Hypogonadotropic hypogonadism is a heterogeneous disease caused by mutations in several genes. Mutations of the β-subunits of LH or FSH and their receptors are causes of HH or sub-HH (Allen, 2003; Hayes, 2013). Rare inactivating mutations that produce distinctive phenotypes of isolated LH or FSH deficiency have been discovered in gonadotropin subunit genes (Themmen, 2000). Females with inactivating mutations of the LH β-subunit present with normal puberty, with normal or late menarche followed by oligo- or amenorrhea and infertility due to lack of ovulation (Lofrano-Porto, 2007). In addition, there are common polymorphism in the LHβ (V-βLH) subunit gene with possible clinical significance as a contributing factor to pathologies of LH-dependent gonadal functions (Themmen, 2000). Worldwide, V-βLH carrier frequency range between from 0% to 52% in various ethnic groups (Lamminen and Huhtaniemi, 2001; Alviggi, 2011) and this polymorphism was also detected in specific gynecological ethnologies as endometriosis (Schmitz, 2015). V-βLH polymorphism affects FSH sensitivity during controlled ovarian stimulation and is

associated with reduced clinical outcomes (Alviggi, 2013). Additionally, polymorphism on LHCGR N312S may impact clinical outcome as well (Ramaraju, 2018).

Most cases of severe LH/FSH deficiency are acquired and can be due to any chronic condition/disorder that acts on the hypothalamic-pituitary axis, including tumors and head injuries but also human immunodeficiency virus (HIV) and diabetes (Hayes et al., 2000). Such conditions may not be reversible. Functional forms of severe LH/FSH deficiency are characterized by a transient defect in GnRH secretion and/or pituitary hormone secretion. This type of presentation occurs often in hypogonadotropic women with transient HA. In susceptible individuals, HA may be precipitated by such factors as significant weight loss, exercise or stress (Laughlin et al., 1998; Warren, 1980). Finally, some drugs, including contraceptive pills and GnRH analogues are iatrogenic causes of hypogonadotropism (Garcia-Velasco et al., 2007; Van Heusden and Fauser, 1999; Kol, 2014, Antoniou-Tsigkos et al., 2018, Physiopathology, Diagnosis, and Treatment of Secondary Female Hypogonadism).

In patients with acquired or functional severe LH/FSH deficiency, GnRH secretion will usually resume after correcting the underlying abnormality whether surgically or by therapeutic therapy, and menstruation will be restored (Hayes et al., 2000).

Incidence:

Considering the heterogeneity of causes and clinical presentations of LH/FSH deficiency, it is not possible to provide a single estimate for the incidence of the condition. Some estimates for specific causes are however available in the published literature.

IHH has an incidence of 1–10 cases per 100,000 births. About 60% of patients with IHH present with associated anosmia, also known as KS (Bianco & Kaiser, 2009). A population-based, epidemiological study from Finland showed a minimal incidence estimate of the KS form of IHH to be 1:48,000 (1:30,000 in males and 1:125,000 in females, respectively) (Laitinen, 2011).

Secondary amenorrhea occurs in approximately 3–5% of adult women. According to the American Society of Reproductive Medicine, functional hypothalamic amenorrhea (FHA) is responsible for 20–35% of secondary amenorrhea cases and approximately 3% of FHA cases of primary amenorrhea. The incidence is higher in women athletes (Meczekalski, 2014).

There is limited data available regarding the incidence and prevalence of hypopituitarism. One study from Spain reported an incidence of 4.2 cases per 100,000 per year and the incidence increased with age (Schneider, 2007).

Prevalence:

GnRH production starts early in fetal life. As a result, gonadotropin levels change drastically during fetal development, childhood, puberty and adulthood. The prevalence of HH has been estimated to range from 1:10,000 to 1:86,000 individuals (Fraietta, 2013).

The prevalence of IHH has been estimated at 1/4,000 to 1/10,000 males, and it is reported to be 2 to 5 times less frequent in females (Della Valle, 2013; Silveira, 2013).

One of the few known studies assessing the prevalence of hypopituitarism, found a prevalence of 45.5 cases per 100,000 in a Spanish population (Schneider, 2007).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Clinical presentation of HH depends on the time of onset, the severity of the defect, and the presence of associated conditions. Usually the diagnosis of congenital IHH is made during the second or third decade of life, when the patients present with delayed pubertal onset, absent or poorly developed secondary sexual characteristics, primary amenorrhea, eunuchoid proportions, or infertility. Adult-onset HH is characterized in women by secondary amenorrhea, decreased libido, infertility, and osteoporosis, whereas in men, symptoms of decreased libido, lack of morning erection, erectile dysfunction, inability to perform vigorous activity, depression, fatigue, and infertility are usually reported (Silveira, 2013).

The main existing treatment options:

Post pubertally, in women with any form of HH, there are three goals to satisfy: (1) correction of the causal factor when feasible, (2) installation or improvement of fertility with ultimate result of a healthy take-home baby, and (3) prevention of the complications related to the pathophysiology of the disease process (e.g., estrogen replacement to prevent osteoporosis) (Antoniou-Tsigkos et al., 2018, Physiopathology, Diagnosis, and Treatment of Secondary Female Hypogonadism).

Based on NICE, women with WHO group I (any form of HH, HA, HP) ovulatory disorders should be counseled to achieve a normal body weight. They may benefit from referral to a physician comfortable with prescribing pulsatile administration of GnRH or gonadotropins with LH activity to induce ovulation (NICE 2013; Lindsay, 2015).

All post-pubertal age patients with KS and IHH are candidates for gonadal steroid replacement therapy in the absence of specific contraindications. Additional therapies to restore fertility can also be implemented. Medical therapies are used to treat associated conditions, including osteoporosis, adrenocortical insufficiency, congenital heart disease, and neurologic disorders. Patients with KS or IHH who do not desire fertility should have gonadal steroid replacement therapy, including testosterone in males and estrogen-progestin in females, unless contraindicated. Fertility options include either GnRH or gonadotropin-based regimens. Clomiphene may also be used in women with hypothalamic amenorrhea (Raivio, 2007).

In patients seeking for pregnancy, although the wide heterogeneity that leads to LH/FSH deficiency, they are all manifested by defects in the hypothalamic-pituitary-ovarian axis and external treatment with gonadotropins are recommended to obtain adequate ovarian function and achieve pregnancy. For the treatment of fertility in women with hypogonadotropic conditions, including severe functional forms, the options are either treatment with pulsatile GnRH, wherever this is possible, or gonadotropin therapy (Antoniou-Tsigkos et al., 2018, Physiopathology, Diagnosis, and Treatment of Secondary Female Hypogonadism). There is no doubt that FSH and LH are needed together to induce ovulation (Raju, 2013).

As described, drugs could lead to functional forms of severe FSH/LH deficiency (Yasmin, 2013; Antoniou-Tsigkos et al., 2018, Physiopathology, Diagnosis, and Treatment of Secondary Female

Hypogonadism). HH functional condition could be reached following GnRH agonists/antagonists' treatment during Medical Assisted Reproduction (MAR) cycles. GnRH analogs enable a reversible block of the gonad-pituitary axis, for preventing premature LH surge. Thus, in this case endogenous FSH/LH secretion is almost blocked. Usually exogenous follitropin stimulating hormone is successfully administered to obtain adequate follicles stimulation. In some cases LH suppression reaches case of severe LH deficiency and the addition of LH is recommended (Rinaldi, 2016; Younis, 2018; Kol, 2014).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

LH and FSH deficiency in women does not entail substantial mortality if there are no associated conditions such as congenital heart disease, neurologic manifestations, brain tumors, cranial radiotherapy, etc. Likewise, KS is not a life-threatening condition. The main features are delayed or absent signs of puberty, and absent or diminished sense of smell (anosmia or hyposmia, respectively).

Congenital severe LH and FSH deficiency in women of childbearing potential is characterized by amenorrhea as its most evident symptom. Amenorrhea is a manifestation of low estrogen production, reduced endometrial thickness and is associated with adverse health conditions like those observed in postmenopausal women. Accordingly, comorbidities associated with female severe LH and FSH deficiency include bone mineral abnormalities, altered lipid profiles, and accelerated cardiovascular disease. Long-term effects of hypogonadism also include an increased risk of developing metabolic problems.

Some studies have suggested an increased risk of reproductive cancers (breast, endothelium, ovaries), possibly associated with infertility and/or its treatment.

Ovarian, endometrial and breast cancers are associated with several risk factors, such as low parity, infertility, early age at menarche, and late age at menopause. Frequently most of these risk factors coexist in infertile patients and some studies suggested that the different infertility causes can be involved in cancer risk development (Cetin, 2008). Since hormonal and reproductive factors are known to be involved in the etiology of cancers of the female reproductive system, a stimulating effect of fertility medications on the risk of these cancers is theoretically possible. Studies looking at rates of breast, endometrial, and ovarian cancers in women receiving fertility treatments have been inconsistent, and most studies have been relatively small. Furthermore, several studies have compared the rate of cancers with the general population when it's known that women treated with assisted reproduction are likely to differ from the general population in their parity, age at first birth, age at menopause (Coney, 2018), and the incidence of predisposing conditions like endometriosis.

Important co-morbidities:

Women with HH anovulation usually present with amenorrhea (Beate, 2012; Messinis, 2005). Amenorrhea is a manifestation of low estrogen production and is associated with adverse health conditions similar to those observed in postmenopausal women. Accordingly, comorbidities

associated with female HH include bone mineral abnormalities, altered lipid profiles, and accelerated cardiovascular disease, etc.

Osteoporosis

Young women with HH are at risk for bone loss and fracture. Congenital hypogonadism may be particularly detrimental to the skeleton because it may lead to failure to achieve peak bone mass, in addition to loss of established bone mass. Measurement of bone mineral density of the lumbar spine, femoral neck, and hip is recommended at the initial diagnosis of HH and after 1 to 2 years of sex steroid therapy in hypogonadal patients with osteoporosis or low trauma fracture (Silveira, 2013).

OHSS (Ovarian hyperstimulation syndrome)

Ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy are the most serious side-effects linked to gonadotropin use (Gibreel, 2010).

Severe OHSS is a potentially life-threatening complication of ovulation induction and has an incidence of about 0.5% to 2%. Polycystic ovarian syndrome (PCOS), previous episodes of OHSS and high doses of exogenous gonadotropins are known to increase the risk of developing OHSS (Gibreel, 2010). Results from studies involving hypogonadotrophic women treated with human gonadotrophins show a very low incidence (~1%) of OHSS but high (up to 30%) multiple pregnancy rates. Similar results were observed when recombinant gonadotrophins were used (Messinis, 2005).

The detrimental impact of endocrinological disorder, which is linked to hyper-secretion of LH and ovulatory dysfunction, is attributed to increased LH levels. Studies have found that such women are associated with poor fertilization, oocyte quality and embryo quality, which could be due to underlying mechanisms such as androgen excess induced by LH. However, contrary to previous belief, it was later demonstrated that hyperinsulinemia and not LH hyper-secretion plays a vital role in PCOS pathogenesis. Adding LH in this scenario would lead to OHSS and hence LH should be avoided (Raju, 2013).

Multiple Pregnancies

Gonadotropin stimulation of the ovaries in assisted reproduction leads to multifollicular growth. Phase III trials of follitropin alpha show a multiple birth rate of 20% when the drug is used for ovulation induction and 35% when it is used in In-Vitro Fertilization (IVF) (Gibreel, 2010). Single embryo transfer is strongly recommended in order to avoid multiple pregnancies by the European Society of Human Reproductive and Embryology (ESHRE) 2015, Penzias et al., 2017 and NICE 2018 with a strong recommendations for patient below the age of 35.

Part II: Module SII Non-clinical Part of the Safety Specification

An extensive program of non-clinical studies was conducted with the two drug substances, r-hFSH and r-hLH, contained in follitropin alfa/lutropin alfa (Pergoveris®) drug product. As the pharmacological properties of r-hFSH and r-hLH are well known, no additional non-clinical pharmacology studies were performed with follitropin alfa/lutropin alfa (Pergoveris®). With

respect to toxicology evaluations, two local tolerance studies with the freeze-dried and the multidose liquid drug product formulations were performed with follitropin alfa/lutropin alfa (Pergoveris®).

The non-clinical safety testing of r-hFSH and r-hLH included studies on safety pharmacology, general toxicity, reproductive and developmental toxicity, in vitro and in vivo mutagenicity and local tolerance.

In vivo investigations of safety pharmacology and toxicology of r-hFSH and r-hLH were investigated in pharmacologically responsive species. Rats and cynomolgus monkeys were used for most non-clinical safety studies and dogs and rabbits were also used for non-clinical safety investigations on the cardiovascular system and on embryo-fetal development respectively.

Key results of the non-clinical safety studies with r-hFSH followed by those with r-hLH and follitropin alfa/lutropin alfa (Pergoveris®) are summarized below:

r-hFSH

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity:	
• **Single and repeat-dose toxicity** In single-dose toxicity studies in rats, dogs and monkeys (refer to studies 4612, 4920, 4613), no signs of systemic toxicity were seen at doses up to 2000-4000 International Unit per Kilogram (IU/kg) by intravenous (iv), intramuscular (im) or subcutaneous (sc) route. In 4-week and 13/52-week repeat-dose toxicity studies in rats by sc route (refer to studies 5335, 5259) and monkeys by im route (refer to studies 5336 and 5258), daily r-hFSH doses up to 1000 IU/kg did not result in systemic toxicity. The changes observed are typical of a response to exogenous or endogenous FSH and represent a primary biological activity of the hormone.	No safety concern for humans has been identified based on the single and repeat-dose toxicity studies performed.
• **Reproductive and developmental toxicity** The fertility of female rats was impaired at r-hFSH doses ≥ 40 IU/kg/day administered by sc route from 14 days prior to the mating period until Day 7 of gestation, through reduced fecundity (refer to study 5261). r-hFSH doses ≥ 5 IU/kg/day administered by sc route during the organogenesis period to pregnant rats and rabbits resulted in a decrease in the number of viable fetuses and dystocia similar to that observed with urinary human Menopausal Gonadotropin (hMG) but without signs of teratogenicity (refer to studies 5262, 5263, 5264).	No safety concern for humans has been identified based on the reproductive and developmental toxicity studies performed.

Key Safety findings (from non-clinical studies)	Relevance to human usage
The Adverse Events (AEs) observed in the reproductive and developmental toxicity studies are due to the hormonal imbalance induced by administration of high doses of such potent gonadotropin (r-hFSH) in the tested animal species.	
• **Genotoxicity** No mutagenic effects of r-hFSH were detected in vitro or in vivo (refer to studies 4608, 4609, 4610, 4611).	No safety concern for humans has been identified based on the genotoxicity studies performed.
• **Carcinogenicity** No carcinogenicity studies were performed considering that r-hFSH is a glycoprotein recombinant form of the endogenous gonadotropin hormone, the lack of genotoxicity, and the very limited period of administration to women).	No potential safety concern for humans has been identified and no carcinogenicity studies in animals were performed.
Safety Pharmacology:	
• **Cardiovascular** (including potential for QT interval prolongation), **and respiratory system** Single iv injection of r-hFSH to anesthetized dogs and rats (refer to studies 5612, 4607) had no significant effect on cardiovascular and respiratory function parameters.	No safety concern for humans has been identified based on the safety pharmacology studies performed.
• **Central Nervous system** No effects on CNS were seen in conscious rats receiving r-hFSH as a single sc administration (refer to study 25683)	No safety concern for humans has been identified based on the safety pharmacology studies performed.
Other toxicity-related information or data:	
• **Local tolerance** Local tolerance of r-hFSH at the site of s.c. or i.m. administration was evaluated within the repeat-dose toxicity studies (refer to studies 4615, 4616, 5335, 5336, 5258 and 5259) and in dedicated studies in the rabbit model (refer to studies 4606 and 20928 for the freeze-dried monodose formulation and to study 23457 for the liquid multi-dose formulation). There was no local tolerance concern in any of the studies.	No safety concern for humans has been identified based on the repeat-dose toxicity studies and the local tolerance studies performed.

r-hLH

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity:	
• **Single and repeat-dose toxicity** In single-dose toxicity studies in rats and monkeys (refer to studies 5750, 5751), no signs of systemic toxicity were seen at doses up to 200,000 IU/kg by intravenous (iv) or subcutaneous (sc) route. In 4-week repeat-dose toxicity studies in rats (refer to studies 5756, 5757) or monkeys (refer to studies 5754 and 5755) daily r-hLH doses up to 5000 IU/kg sc or iv did not result in systemic toxicity. No signs of systemic toxicity were seen in 13-week repeat dose toxicity studies in female rats and female monkeys (refer to studies 6586, 6587) with daily r-hLH doses up to 1000 IU/kg sc. The observed Adverse Events (AEs) could mainly be attributed to excessive steroid hormone production subsequent to administration of high doses of r-hLH.	No safety concern for humans has been identified based on the single and repeat-dose toxicity studies performed.
• **Reproductive and developmental toxicity** Increases in pre-and post-implantation losses (at r-hLH doses ≥ 10 IU/kg/day sc), a lowered fertility index and decreases of mean fetal weight (at 20 IU/kg/day sc) were detected in a rat fertility study (refer to study 7099). r-hLH doses ≥ 10 IU/kg/day s.c. administered during the organogenesis period to rats and rabbits (refer to studies 7100, 7101) increased fetal resorption rate and decreased (in rats) the number of viable fetuses. No teratogenic effects were seen in either species. In a pre- and postnatal study in rats (refer to study 7098), an increase in pre- and postnatal mortality of pups occurred at doses ≥ 10 IU/kg/day sc. The Adverse Events (AEs) in the reproductive and developmental toxicity studies are due to the hormonal imbalance induced by administration of high doses of such potent gonadotropin (r-hLH) in the tested animal species.	No safety concern for humans has been identified based on the reproductive and developmental toxicity studies performed.
• **Genotoxicity** No mutagenic effects of r-hLH were detected in vitro or in vivo (refer to studies 5740, 5741, 5742, 5743).	No safety concern for humans has been identified based on the genotoxicity studies performed.
• **Carcinogenicity** No carcinogenicity studies were performed considering that r-hLH is a glycoprotein recombinant form of the endogenous gonadotropin hormone, the lack of genotoxicity, and the very limited period of administration to women).	No potential safety concern for humans has been identified and no carcinogenicity studies in animals were performed.
Safety pharmacology:	
• **Cardiovascular** (including potential for QT interval prolongation), **and respiratory system**	

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single iv injection of r-hLH to anesthetized dogs had no significant effect on cardiovascular and respiratory function parameters (refer to study 5752).	No safety concern for humans has been identified based on the safety pharmacology studies performed.
• **Central Nervous system** No effects on CNS were seen in conscious mice or rats receiving r-hLH as a single sc administration (refer to study 6525).	No safety concern for humans has been identified based on the safety pharmacology studies performed.
Other toxicity-related information or data:	
• **Local tolerance** Local tolerance of r-hLH at the injection site was evaluated within the repeat-dose toxicity studies (studies 5754, 5756, 6586 and 6587) after s.c. administrations and in dedicated local tolerance studies in the rabbit model after im administration (refer to study 5753) and after im and sc administration (refer to study 22178). There was no local tolerance concern in any of the studies.	No safety concern for humans has been identified based on the repeat-dose toxicity studies and the local tolerance studies performed.

Pergoveris® (r-hFSH and r-hLH)

With respect to the non-clinical safety assessment of follitropin alfa/lutropin alfa (Pergoveris®), reference is made to the studies conducted on the two individual drug substances, r-hFSH and r-hLH, contained in Pergoveris® drug product. The local tolerance of the freeze-dried and the multi-dose liquid drug product formulations was additionally evaluated in two dedicated animal studies.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity:	
• **Single and repeat-dose toxicity** Single and repeat-dose toxicity studies were conducted on the two individual drug substances, r-hFSH and r-hLH, contained in Pergoveris® drug product (see tabulated summaries of r-hFSH and r-hLH above).	No safety concern for humans has been identified based on the single and repeat-dose toxicity studies performed.
• **Reproductive and developmental toxicity** Reproductive and developmental toxicity studies were conducted on the two individual drug substances, r-hFSH and r-hLH, contained in the Pergoveris® drug product (see tabulated summaries of r-hFSH and r-hLH above). The Adverse Events (AEs) in the reproductive and developmental toxicity studies are due to the hormonal imbalance induced by administration of high doses of such potent gonadotropins (r-hFSH or r-hLH) in the tested animal species.	No safety concern for humans has been identified based on the reproductive and developmental toxicity studies performed. There is no indication for use of Pergoveris® in pregnancy.
• **Genotoxicity** Genotoxicity studies were conducted on the two individual drug substances, r-hFSH and r-hLH, contained in the Pergoveris® drug product (see tabulated summaries of r-hFSH and r-hLH above)	No safety concern for humans has been identified based on the genotoxicity studies performed.

Key Safety findings (from non-clinical studies)	Relevance to human usage
• **Carcinogenicity** No carcinogenicity studies were performed on the two individual drug substances, r-hFSH and r-hLH, contained in the Pergoveris® drug product or with their combination (r-hFSH and r-hLH glycoprotein recombinant forms of the endogenous gonadotropin hormones, lack of genotoxicity, and very limited period of administration to women).	No potential safety concern for humans has been identified and no carcinogenicity studies in animals were performed.
Safety pharmacology:	
• **Cardiovascular** (including potential for QT interval prolongation), **and respiratory system** Safety pharmacology investigations on cardiovascular and respiratory systems were conducted on the two individual drug substances, r-hFSH and r-hLH, contained in the Pergoveris® drug product (see tabulated summaries of r-hFSH and r-hLH above).	No safety concern for humans has been identified based on the safety pharmacology studies performed.
• **Central Nervous system** Safety pharmacology investigations on CNS were conducted on the two individual drug substances, r-hFSH and r-hLH, contained in the Pergoveris® drug product (see tabulated summaries of r-hFSH and r-hLH above).	No safety concern for humans has been identified based on the safety pharmacology studies performed.
Other toxicity-related information or data:	
• **Local tolerance** The extensive toxicology program performed with the individual drug substances, r-hFSH and r-hLH, contained in Pergoveris® drug product included local tolerance evaluation at the site of sc administration within the repeat-dose toxicity studies. Local tolerance of Pergoveris® drug product was evaluated in dedicated studies in the rabbit animal model, as summarized below: • Pergoveris® freeze-dried formulation (containing 150 IU r-hFSH and 75 IU r-hLH) was very well tolerated locally after a single and after repeated (7-day) sc injections (refer to study 23595) • Pergoveris® multi-dose liquid formulation (containing 625 International Units per Milliliter (IU/mL) r-hFSH and 312.5 IU/mL r-hLH) was very well tolerated locally after a single and after repeated (7-day) sc injections at a dose of 150 IU r-hFSH and 75 IU r-hLH (refer to study 14-IV113-N0).	No safety concern for humans has been identified based on the repeat-dose toxicity studies performed with the individual drug substances, r-hFSH and r-hLH, contained in Pergoveris® drug product and the local tolerance studies performed with the. Pergoveris® drug product.

Part II: Module SIII Clinical Trial Exposure

Pergoveris® corresponds to the fixed combination of 2 drug substances (follitropin alfa and lutropin alfa) already in widespread use. Both follitropin alfa and lutropin alfa are currently individually available on the market with the trade names Gonal-f® and Luveris®, respectively. Thus, to support the registration of Pergoveris®, the Pharmacokinetics/Pharmacodynamic (PK/PD) studies conducted for follitropin alfa and lutropin alfa as well as several studies using a combination of follitropin alfa and lutropin alfa at the same doses as in Pergoveris® were

considered. A total of 4 bioequivalence studies (23718, 23722, 28781 and EMR 200061-004) and one general PK study (EMR 200031-002) were performed. A bioequivalence study with a newly developed liquid formulation (EMR 200061-006) was also conducted.

The outcome of the bioequivalence studies showed that:

1) r-hFSH in Pergoveris® is bioequivalent to follitropin alfa in Gonal-f® indicating that all PK/PD characteristics of r-hFSH in Pergoveris® are similar to the PK/PD characteristics of follitropin-alfa in Gonal-f® and,

2) r-hLH in Pergoveris® is bioequivalent to lutropin alfa in Luveris® indicating that all PK/PD characteristics of r-hLH in Pergoveris® are similar to the PK/PD characteristics of lutropin alfa in Luveris®.

3) Liquid formulation is bioequivalent to freeze dried formulation, with no significant difference in tolerability.

List of Phase I Pharmacokinetics and bioequivalence on the fixed combination of r-hFSH/r-hLH (150 IU/75 IU) are presented below. A total of six Phase I studies, age group of 18 to 40 years, were conducted using fixed combination of r-hFSH/r-hLH (150 IU/75 IU) in 248 healthy female subjects.

Table 1 Phase I studies using the Fixed Combination of r-hFSH/r-hLH (150 IU/75 IU)

Study	Phase and study type	Dose (IU)	Age group	No. of Subjects received r-hFSH/r-hLH
23718	Phase I - bioequivalence	300 IU of r-hFSH and 150 IU of r-hLH from vials of r-hFSH (150 IU) and r-hLH (75 IU) in fixed combination was compared with Gonal-f® (300 IU)	18-33 years	35
23722	Phase I - bioequivalence	900 IU of r-hFSH and 450 IU of r-hLH from vials of r-hFSH (150 IU) and r-hLH (75 IU) in fixed combination and Luveris® (450 IU from vials of 75 IU)	18-40 years	73
28781	Phase I - bioequivalence	Pergoveris® liquid formulation (900 IU r-hFSH/450 IU r-hLH) with freeze-dried formulation of Pergoveris® (900 IU r-hFSH/450 IU r-hLH)	18-40 years	44
EMR 200031-002	Phase I - Pharmacokinetics	r-hFSH after the administration of Pergoveris® (freeze-dried) at dose of 300/150 IU, 450/225 IU and 900/450 IU	18-40 years	18
EMR 200061-004	Phase I - bioequivalence	Fixed combination of Pergoveris® (freeze-dried) 900 IU r-hFSH and 450 IU r-hLH versus 900 IU of r-hFSH (Gonal-f®) and 450 IU of r-hLH (Luveris®)	18-40 years	44
EMR 200061-006	Phase I - bioequivalence	Pergoveris® liquid formulation (900 IU r-hFSH/450 IU r-hLH) with freeze-dried formulation of Pergoveris® (900 IU r-hFSH/450 IU r-hLH)	18-40 years	34
Total subject exposure				**248**

The below table presents clinical studies (Phase II to IV) conducted using r-hFSH and r-hLH for ovulation induction and assisted reproductive technology (ART) including in vitro fertilization/embryo transfer. In total 19 clinical studies (seven for OI and 12 for ART Phase II – IV were conducted using r-hFSH and r-hLH in approximately 2,296 female subjects. In majority of studies, the subject age ranged from 18-40 years. In two studies (21875 and 27262) the female subjects older than 40 years (≤ 42) were included.

Table 2 Phase II – IV - Clinical Studies Using r-hFSH/r-hLH in Ovulation Induction, and Assisted Reproductive Technologies, including IVF/ET

Study	Phase and study type	Dose (IU)	Age group	Subject group/indication	No. of subjects received r-hFSH/r-hLH
Ovulation Induction					
GF6253	Phase II/III, dose-finding, efficacy/safety	r-hLH:0, 25, 75, 225 IU r-hFSH: 150IU (fixed)	18-33 years	Anovulatory women	38
GF6905	Phase II/III, dose-finding, efficacy/safety	r-hLH: 0, 25, 75, 225 IU r-hFSH: 150 (fixed)	18-40 years	Anovulatory women	29
GF7798	Phase III, efficacy/ safety	r-hLH: 75, 150, 225 IU r-hFSH: 150 IU (fixed)	18-39 years	Anovulatory women	15
GF8297	Phase III, efficacy/ safety	r-hLH: 75, 150, 225 IU r-hFSH: 75 IU (fixed)	18-35 years	Anovulatory women	38
21008	Phase III efficacy/safety	r-hLH 0.75 IU r-hFSH: 150 IU (fixed)	18-39 years	Anovulatory women	27
21415	Phase III efficacy/safety (follow up of IMP 21008)	r-hLH 75 IU r-hFSH 75-225 IU	18-39 years	Anovulatory women	31*
26109 (Terminated)	Phase IV efficacy/ safety (PAC* program)	r-hLH 0,25,75 IU r-hFSH 75 IU	18-40 years	Induction of follicular development & pregnancy in HH women with profound LH deficiency	11
Assisted Reproductive Technologies, including IVF/ET					
9261	Phase III – efficacy/safety comparing r-hFSH alone with r-hFSH + r-hLH	r-hLH: 150 r-hFSH: 225	18-40 years	ART: stimulation of follicular development prior to intra cytoplasmic sperm injection (ICSI)	212
21875	Phase II – dose ratio finding, efficacy/safety	Starting doses of r hLH: 225 IU, 112.5 IU, 75 IU, 0 IU, r-hFSH: 225 administered in 4 fixed r hFSH:r hLH dose-ratios: 1:1, 2:1, 3:1 & 1:0	38-42 years	IVF/ET: stimulation of follicular development	127

Study	Phase and study type	Dose (IU)	Age group	Subject group/indication	No. of subjects received r-hFSH/r-hLH
GF9007	Phase III - Efficacy/safety of r-hLH	r-hLH: ≤ 75 r-FSH: ≤ 375	18-39 years	IVF: stimulation of follicular development, late follicular phase	792
GF9029	Phase II/III – efficacy/safety comparing r-hFSH alone with r-hFSH + r-hLH	r-hLH: 75 r-FSH: 450	18-38 years	IVF/ET: stimulation of follicular development in poor responders	23
GF9032	Phase II/III efficacy/safety comparing r-hFSH alone with r-hFSH + r-hLH	r-hLH: 75 r-hFSH: 225-450	35-40 years	IVF/ET: stimulation of follicular development	22
25186	Phase II efficacy/safety comparing r-hFSH alone with r-hFSH + r-hLH	r-hLH: 150 r-hFSH: 150-450	35-40 years	ART: stimulation of follicular development prior to ICSI	63
25244	Phase III – efficacy/safety of r-hLH	r-hLH; 150 r-hFSH: 150	18-40 years	ART: stimulation of follicular development	52
25289	Phase III – efficacy/safety comparing r-hFSH alone with r-hFSH + r-hLH	≤150 IU, with FSH: LH at 2:1	18-40 years	ART: stimulation of follicular development in patients who required a high FSH dose in a previous cycle	67
26170	Phase II – efficacy/safety comparing r-hFSH alone with r-hFSH + r-hLH	r-hLH/r-hFSH; 150	≤ 38 years	ART: stimulation of follicular development prior to ICSI in women at risk of low response	16
27262	Phase II - efficacy/safety of mid follicular addition of r-hLH vs. no addition of r-hLH	r-hLH/r-hFSH; 150	35-42 years	Controlled ovarian stimulation with r-hFSH under GnRH antagonist protocol prior to IVF-ICSI	97

Study	Phase and study type	Dose (IU)	Age group	Subject group/indication	No. of subjects received r-hFSH/r-hLH
EMR 200061-504	Phase III - the efficacy and safety of ovarian stimulation with Gonal- f® day 1 to day 5 followed by Pergoveris®	r-hFSH 300 vs r-FSH/r-hLH: 150/75	36-40 years	ART: stimulation of follicular development	202
EMR200061-005	Phase III – the efficacy and safety of Pergoveris® and Gonal-f®	150 r-hFSH and 75 r-hLH and 450 r-hFSH	18 to < 41 years	ART: stimulation of follicular development	462
Total subject exposure					**2,297**

*In study 21008, 39 subjects received r-hFSH of which only 27 subjects received r-hFSH and r-hLH. Subjects in study 21415 were from study 21008. Considering that 27 subjects are already counted in study 21008, only 4 patients have been included in the total subject exposure.

The overall estimated subject exposure from Phase I to IV was 2,545 (248 in Phase I and 2,297 in Phase II-IV) female subjects. Of these subjects, 2,321 were in the 18-40 years age group and 224 in 35-42 years age group (study 21875 and 27262).

Note: The clinical data presented in the RMP is accurate to the Company's best knowledge and includes all subjects in every known clinical trial.

Part II: Module SIV Populations not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

In accordance with the Guideline on good pharmacovigilance practices (GVP) – Module V Risk Management Systems, Module SIV is not required as:

- Pergoveris® is a fixed combination product composed of follitropin alfa (Gonal-f®) and lutropin alfa (Luveris®).
- Pergoveris® was placed on the market more than 10 years before the requirement of RMP was established (centralized EU authorization in 25 June 2007).
- The requirement for RMP is not due to an application for a significant change to an existing marketing authorization.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

Not applicable

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Not applicable

Part II: Module SV Post-Authorization Experience

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

It is difficult to estimate the number of treated women from the sales volume as the duration of treatment and the dose are individualized for each patient. Therefore, the treatment-cycle is considered to be the most relevant denominator for calculating the patient's exposure.

The Company routinely collects worldwide sales data for Pergoveris®. An estimate of the number of treatment-cycles performed with Pergoveris® was calculated from the sales volume until the Data Lock Point (DLP) of this RMP (30 April 2019), taking into account the following:

It was assumed that one vial of Pergoveris® (150/75 IU) is administered per day and per patient and that the average length of one cycle is 12 days (i.e. duration of one treatment-cycle).

Thus, the number of treatment-cycles = total number of sold vials / 12.

For Pergoveris® cartridges (300/150 IU, 450/225 IU and 900/450 IU) for pre-filled pens, treatment-cycles were calculated by converting each cartridge strength into a single vial of 150/75 IU. Hence, Pergoveris® 300/150 IU is equivalent to two vials of 150/75 IU, 450/225 IU is equivalent to three vials and 900/450 IU is equivalent to six vials.

SV.1.2 Exposure

Taking into consideration the aforementioned assumptions and sale volumes over the review period, the estimated cumulative patient exposure in the post-marketing setting to Pergoveris® since granting of the first marketing authorization in 25 June 2007 until the DLP of the RMP was 808,940 treatment-cycles.

Part II: Module SVI Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

In males, LH stimulates the production of androgens, particularly testosterone by binding on the testicular Leydig cells.

This LH-stimulated testosterone release from Leydig cells may in turn stimulate accessory sexual organs (seminal vesicles) and body weight gain as a consequence of an anabolic growth-promoting effect.

This effect has also been described for hCG and both hormones (hCG and LH) have been reported as being potentially used to enhance the endogenous production of testosterone (Kicman & Cowan, 1992) by artificial means.

The Medical Commission of the International Olympic Committee (IOC) even introduced in 1989 the new doping class of peptide hormones and analogues, in which hCG and related compounds, Adreno CorticoTropic Hormone (ACTH), human growth hormone (hGH), all the releasing factors of these listed hormones as well as erythropoietin (EPO) are included. The theoretical risk of misuse of Pergoveris® for illegal purpose is minimal, as Pergoveris® is not only LH but a combination of LH and FSH. Additionally, the product is available only under prescription and because the sportsmen and women who abuse hormones prefer hCG, particularly the urinary-derived product, which is much cheaper.

Part II: Module SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable as this RMP version is not the initial submitted RMP.

SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

"Ovarian Hyperstimulation Syndrome (OHSS)" and "Thromboembolic events, usually with OHSS" and "Hypersensitivity reactions" previously classified as important identified risks were removed from the list of safety concerns.

"Breast cancer", "Ovarian cancer", "Endometrial cancer", "Congenital anomalies" and "Malignant melanoma" previously classified as important potential risks were removed from the list of safety concerns.

The missing information of "Premenopausal women with severe LH and FSH deficiency older than 42 years" was removed from the list of safety concerns.

Reasons for the removal of the above risks from the list of safety concerns:

Important Identified Risks:

Ovarian Hyperstimulation Syndrome (OHSS):

OHSS is an iatrogenic complication of ovarian stimulation usually occurring during the luteal phase or during the early part of pregnancy. The incidence for OHSS varies for different treatment and patient groups. It is difficult to get true estimates from literature since often different criteria for diagnosis and classifications for severity are used.

"Ovarian Hyperstimulation Syndrome (OHSS)" was proposed as an important identified risk for follitropin alfa/lutropin alfa (Pergoveris®) by the Company in the RMP version 1.0 (dated March 2006) approved by the European Medicines Agency (EMA). In the RMP version 2.0 (dated 18 August 2009, EMA/765635/2009), the risk was reclassified as an important potential risk by the Company. However, as per the Pharmacovigilance Risk Assessment Committee (PRAC) assessor's recommendation, the risk was again reclassified as an important identified risk for follitropin alfa/lutropin alfa (Pergoveris®) in the RMP version 3.0 (dated 14 February 2010, EMA/342556/2010) approved by the EMA.

Characterization of the risk

The Company considers the important identified risk of "OHSS" as fully characterized up to the DLP of the RMP version 5.3 (30 April 2019).

Overview of the important identified risk of OHSS:

Safety concern	**Ovarian Hyperstimulation Syndrome (OHSS)**
Reason of initial addition of the risk	Proposed by the Company
Safety concern included in Pergoveris® European Union-Summary of Product Characteristics (EU-SmPC)	• Section 4.4 "Special Warnings and Precautions for Use" • Section 4.8 "Undesirable Effects" • Section 4.9 "Overdose"

Frequency	**Frequency as per Pergoveris® EU-SmPC**	• Common (≥1/100 to <1/10): mild or moderate OHSS • Uncommon (≥1/1000 to <1/100): severe OHSS • Rare (≥1/10,000 to <1/1,000): complication of severe OHSS
	Cumulative reporting rate up to the DLP of RMP v5.3 i.e. 30 April 2019	8.8 per 100,000 treatment-cycles
	Cumulative reporting rate per Periodic Benefit Risk Evaluation Report (PBRER) period 20 October 2015 to 19 October 2018	9.4 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER, 25 June 2011 - 19 Oct 2015	9.2 per 100,000 treatment-cycles
Pharmacovigilance plan		**Routine pharmacovigilance activities:** Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) are considered sufficient for monitoring the safety concern of the medicinal product. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaires for safety concern: None Other forms of routine pharmacovigilance activities for safety concern: None **Additional pharmacovigilance activities:** None
Risk minimization measures		**Routine risk minimization activities:** Routine risk communication: OHSS is listed as an adverse reaction [EU-SmPC section 4.8 and Package Leaflet (PL) section 4]. Statement of a possibility that OHSS may occur following an overdose (EU-SmPC section 4.9 and PL section 3). Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations to adhere to Pergoveris® dosage and regimen of administration (SmPC section 4.4 and PL section 2). • Recommendation to carefully monitor stimulation cycle by ultrasound and estradiol measurements to minimize the risk of OHSS (SmPC section 4.4). • Recommendation to withhold hCG administration and the patient be advised to refrain from coitus or to use barrier contraception for at least 4 days, if signs of ovarian hyperstimulation occur (EU-SmPC section 4.4 and PL section 2). • Recommendation to follow patients for at least two weeks after hCG administration (EU-SmPC section 4.4). • Recommendation to stop gonadotropin treatment in case of severe OHSS (EU-SmPC section 4.4). Other routine risk minimization measures beyond the Product Information:

	Legal status: Prescription only medicine **Additional risk minimization activities:** None

Evaluation for the removal of the risk:

The Company proposes to remove the risk of "OHSS" as there has been no new safety information in the last 7 years which could further characterize this risk. In order to support the recommendation, the Company has summarized the last 7 years of data from safety reports i.e., PBRERs from 25 June 2011 to 19 October 2015 and 20 October 2015 to 19 October 2018:

- "Mild or moderate OHSS (including associated symptomatology)" is listed as common (≥1/100 to<1/10), severe OHSS (including associated symptomatology) as uncommon (≥1/1,000 to <1/100), and complication of severe OHSS is considered as rare (≥1/10,000 to <1/1,000) in Section 4.8 (Undesirable Effects) of the follitropin alfa/lutropin alfa (Pergoveris®) EU-SmPC.
- In comparison to the frequency of "OHSS" mentioned in the follitropin alfa/lutropin alfa (Pergoveris®) EU-SmPC, the frequency of "OHSS" Individual Case Safety Reports (ICSRs) received by the Company in the post-marketing experience have remained low over the last 7 years i.e. very rare (<1/10,000).
- No change in the severity or seriousness of "OHSS" which could constitute a new safety finding has been observed.
- There has been no new relevant safety information from the clinical trials or literature surveillance.
- The information concerning "OHSS" in the EU-SmPC for follitropin alfa/lutropin alfa (Pergoveris®) has not changed and has remained adequate.
- Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) have been considered adequate for monitoring of the risk in relation to treatment with follitropin alfa/lutropin alfa (Pergoveris®). No additional pharmacovigilance activities have been undertaken by the Company for this risk.

Risk minimization measures for the safety concern:

The Company considers that the current risk minimization measures for "OHSS" are adequate in the follitropin alfa/lutropin alfa (Pergoveris®) EU-SmPC; there have been no additional risk minimization activities for this safety concern for over 7 years.

The Company considers that the risk minimization activities recommending specific clinical measures for the risk are part of standard clinical practice. The following best practice measures have been recommended with a view to helping minimize the risk of OHSS [Royal College of Obstetricians and Gynecologists (RCOG)-UK Guidelines 2016; Practice Committee ASRM, 2016; Whelan, 2000; Mathur et al., 2000)]:

- Identify women at high risk of developing OHSS (polycystic ovary, young age, low body mass index, previous history of OHSS).

- Start treatment with the lowest effective dose with a cautious increase in dose in cases of insufficient response.
- Monitoring of OI cycles: by ultrasound and / or serum estradiol levels (E2) for rapidly rising E2 levels, high E2 level prior to hCG administration, and appearance of large number of intermediate sized (10-14 mm) follicles.
- In case of signs of ovarian overstimulation withhold further gonadotropin as well as hCG administration or delay hCG until E2 levels decrease (coasting). Advise the patient to refrain from coitus or use barrier methods for at least 4 days.
- To administer lowest effective dose of hCG in all cases especially in high risk women defined above.
- The patients receiving follitropin alfa/lutropin alfa (Pergoveris®) should be instructed to report any abdominal pain immediately and a pelvic examination plus ultrasound should be performed to determine whether or not ovarian enlargement has occurred. As OHSS can progress rapidly (within 24 hours) or over several days to become a serious medical event, patients should be followed for at least 2 weeks following hCG administration.

Conclusion:

Follitropin alfa/lutropin alfa (Pergoveris®) has a large global patient exposure (808,940 treatment-cycles up to 30 April 2019) and has been authorized in the EU since 25 June 2007. The ICSRs pertaining to the risk of "OHSS" with the use of follitropin alfa/lutropin alfa (Pergoveris®) have been reported very rarely (<1/10,000) in the Company safety database for over 7 years, and the reporting rates have remained lower than the frequency mentioned in the follitropin alfa/lutropin alfa (Pergoveris®) EU-SmPC. No additional pharmacovigilance activities and additional risk minimization activities have been conducted for this risk. Furthermore, the Company considers that the risk is fully characterized and does not expect that any pharmacovigilance activities can further characterize the risk. As mentioned above, the Company believes that the risk minimization activities recommending specific clinical measures to address the risk are fully integrated into standard clinical practice. Hence, the Company proposes to remove "OHSS" as an important identified risk. The Company will continue to perform routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection activities).

<u>Thromboembolic events, usually with OHSS:</u>

"Thromboembolic events (TE), usually with OHSS" was initially proposed as an important potential risk by the Company in the RMP version 2.0 (dated 18 August 2009, EMA/765635/2009). However, as per the PRAC assessor's recommendation, the risk was reclassified as an important identified risk for follitropin alfa/lutropin alfa (Pergoveris®) in the RMP version 3.0 (dated 14 February 2010) approved by the EMA.

Characterization of the risk

The Company considers the important identified risk of "Thromboembolic events, usually with OHSS" as fully characterized up to the DLP of the RMP version 5.3 (30 April 2019).

Overview of the important identified risk of thromboembolic events, usually with OHSS

Safety concern		**Thromboembolic events, usually with OHSS**
Reason of initial addition of the risk		Proposed by the Company
Safety concern included in Pergoveris® EU-SmPC		• Section 4.4 “Special Warnings and Precautions for Use” • Section 4.8 “Undesirable Effects”.
Frequency	**Frequency as per Pergoveris® EU-SmPC**	• Very rare (<1/10,000)
	Cumulative reporting rate up to the DLP of RMP v5.3 i.e. 30 April 2019	0.0 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER period 20 October 2015 to 19 October 2018	0.0 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER, 25 June 2011 - 19 Oct 2015	0.0 per 100,000 treatment-cycles
Pharmacovigilance plan		**Routine pharmacovigilance activities:** Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) are considered sufficient for monitoring the safety concern of the medicinal product. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaires for safety concern: None Other forms of routine pharmacovigilance activities for safety concern: None **Additional pharmacovigilance activities:** None
Risk minimization measures		**Routine risk minimization activities:** Routine risk communication: Thromboembolism listed as an adverse reaction (EU-SmPC section 4.8 ad PL section 4). Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations provided to carefully weigh treatment benefit versus the risk of thromboembolic events in predisposed patients (EU-SmPC section 4.4 and PL section 2). Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine **Additional risk minimization activities:** None

Evaluation for the removal of the risk:

The Company proposes to remove the risk of "Thromboembolic events, usually with OHSS" as there has been no new information in the last 7 years which could further characterize this risk. In order to support the recommendation, the Company has summarized the last 7 years of data from safety reports i.e., PBRERs covering the periods of 25 June 2011 to 19 October 2015 and 20 October 2015 to 19 October 2018:

- "Thromboembolism, usually associated with severe OHSS" is listed as very rare (<1/10,000) in Section 4.8 (Undesirable Effects) of the follitropin alfa/lutropin alfa (Pergoveris®) EU-SmPC. Furthermore, the risk of TEs is adequately addressed in Section 4.4 (Special Warnings and Precautions for Use) of follitropin alfa/lutropin alfa (Pergoveris®) EU-SmPC.
- Cumulatively up to the DLP of the RMP version 5.3 (30 April 2019), no cases of "Thromboembolic events, usually with OHSS" have been reported to the Company.
- There has been no new relevant safety information from clinical trials or literature surveillance.
- The information concerning "Thromboembolic events, usually with OHSS" in the EU-SmPC for follitropin alfa/lutropin alfa (Pergoveris®) has not changed and has remained adequate.
- Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) have been considered adequate for monitoring of the risk in relation to treatment with follitropin alfa/lutropin alfa (Pergoveris®). No additional pharmacovigilance activities have been undertaken by the Company.

Risk minimization measures for the safety concern:

The Company considers that the current risk minimization measures for "Thromboembolic events, usually with OHSS" are adequate in the follitropin alfa/lutropin alfa (Pergoveris®) EU-SmPC; there have been no additional risk minimization activities for this safety concern for over 7 years.

In women with generally recognized risk factors for TEs, the benefits of gonadotrophin administration should be weighed against the risks. It should be noted that pregnancy itself also carries an increased risk of TEs (Villani et al., 2018). The recognition of OHSS and rapid supportive management of patients developing the syndrome is the key in preventing the possible devastating development of severe thromboses (Chan and Dixon, 2008). Furthermore, in the 2016 guideline by the American Society for Reproductive Medicine (ASRM) (Practice Committee ASRM, 2016) on the prevention and treatment of moderate and severe OHSS, it is mentioned that prophylactic anticoagulation to treat arterial or venous thromboembolism is warranted in cases of severe OHSS from the time of diagnosis through the first trimester of pregnancy (Practice Committee ASRM, 2016).

Conclusion:

Follitropin alfa/lutropin alfa (Pergoveris®) has a large global patient (women) exposure (808,940 treatment-cycles as of 30 April 2019 and has been authorized in the EU since 25 June 2007. No cases pertaining to the risk of "Thromboembolic events, usually with OHSS" with the use of follitropin alfa/lutropin alfa (Pergoveris®) have been reported to the Company. No additional pharmacovigilance activities and additional risk minimization activities have been conducted for

this risk in the last 7 years. Furthermore, the Company considers that the risk is fully characterized and does not expect that any pharmacovigilance activities can further characterize the risk. As mentioned above, the Company believes that the risk minimization activities recommending specific clinical measures to address the risk are fully integrated into standard clinical practice. Hence, the Company proposes to remove "Thromboembolic events, usually with OHSS" as an important identified risk. The Company will continue to perform pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection activities).

Hypersensitivity reactions

The Company proposed the risk of "Allergic reactions" as an important identified risk for follitropin alfa/lutropin alfa (Pergoveris®) in the RMP version 1.0 (dated March 2006) approved by the EMA. In the RMP version 2.0 (dated 18 August 2009), the risk was reclassified as an important potential risk and the terminology was changed to "Hypersensitivity reactions". However, as per the PRAC assessor's recommendation, "Hypersensitivity reactions" was again reclassified as an important identified risk for follitropin alfa/lutropin alfa (Pergoveris®) in the RMP version 3.0 (dated 14 February 2010) approved by the EMA.

Hypersensitivity is a frequent condition in the general population involving a myriad of possible allergens. The severity of hypersensitivity reactions may vary from mild to severe forms and the nature of the risk depends on multitude factors, such as the time of exposure (first versus second exposure), the patient's history and underlying conditions. Hypersensitivity mechanism is well described in the literature. Any drug is assumed to be able to induce a hypersensitivity reaction. Drug hypersensitivity reactions may comprise allergic (via an IgE mediated process) and/or, so called, pseudoallergic reactions (i.e., via a direct toxic effect on the mast cells and basophils leading to histamine release).

Characterization of the risk

The Company considers the important identified risk of "Hypersensitivity reactions" as fully characterized up to the DLP of the RMP version 5.3 (30 April 2019).

Overview of the important identified risk of hypersensitivity reactions

Safety concern		**Hypersensitivity reactions**
Reason of initial addition of the risk		Proposed by the Company
Safety concern included in Pergoveris® EU-SmPC		• Section 4.3 "Contraindications" • Section 4.8 "Undesirable effects".
Frequency	**Frequency as per Pergoveris® EU-SmPC**	• Very rare (<1/10,000)
	Cumulative reporting rate up to the DLP of RMP v5.3 i.e. 30 April 2019	3.5 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER period 20 October 2015 to 19 October 2018	4.1 per 100,000 treatment-cycles

	Cumulative reporting rate per PBRER, 25 June 2011 - 19 Oct 2015	6.7 per 100,000 treatment-cycles
Pharmacovigilance plan		**Routine pharmacovigilance activities:** Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) are considered sufficient for monitoring the safety concern of the medicinal product. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaires for safety concern: None Other forms of routine pharmacovigilance activities for safety concern: None **Additional pharmacovigilance activities:** None
Risk minimization measures		**Routine risk minimization activities:** Routine risk communication: Mild to severe hypersensitivity reactions including anaphylactic reactions and shock listed as adverse reaction (EU-SmPC section 4.8 and PL section 4). Routine risk minimization activities recommending specific clinical measures to address the risk: Instruction to clinically assess and rule out patients with pre-existing hypersensitivity to the active substance or to any of the excipients of Pergoveris® before starting treatment (SmPC section 4.3 and PL section 2). Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine **Additional risk minimization activities:** None

Evaluation for the removal of the risk:

The Company proposes to remove the risk of "Hypersensitivity reactions" as there has been no new information in the last 7 years which could further characterize this risk. In order to support this recommendation, the Company has summarized data from the last two PBRERs covering the period 2011-2018 (i.e. 25 June 2011 to 19 October 2015 and 20 October 2015 to 19 October 2018):

- "Mild to severe hypersensitivity reactions including anaphylactic reactions and shock" is listed as very rare (<1/10,000) in Section 4.8 (Undesirable Effects) of the follitropin alfa/lutropin alfa (Pergoveris®) EU-SmPC.
- The reporting rates for "Hypersensitivity reactions" have remained very rare i.e. <1/10,000, which is same as the frequency mentioned in the current follitropin alfa/lutropin alfa

(Pergoveris®) EU-SmPC. Additionally, there has been no increase in the cumulative reporting rates overtime.

- No change in the severity or seriousness of outcomes of "Hypersensitivity reactions" which could constitute a new safety finding has been observed.
- There has been no new relevant safety information from clinical trials or literature surveillance.
- The information concerning "Hypersensitivity reactions" in the follitropin alfa/lutropin alfa (Pergoveris®) EU-SmPC has not changed and has remained adequate.
- Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) have been considered adequate for monitoring the risk in relation to treatment with follitropin alfa/lutropin alfa (Pergoveris®). No additional pharmacovigilance activities have been undertaken by the Company.

Risk minimization measures for the safety concern:

The Company considers the current risk minimization measures for "Hypersensitivity reactions" are adequate. There have been no additional risk minimization activities for this safety concern for over 7 years. Furthermore, the product is contraindicated in patients with known hypersensitivity to the active substance or any of the excipients of follitropin alfa/lutropin alfa (Pergoveris®).

Conclusion:

Follitropin alfa/lutropin alfa (Pergoveris®) has a large global patient exposure (808,940 treatment-cycles as of 30 April 2019) and has been authorized in the EU since 25 June 2007. The ICSRs pertaining to the risk of "Hypersensitivity reactions" with the use of follitropin alfa/lutropin alfa (Pergoveris®) have been reported very rarely (< 1/10,000) in the Company safety database for over 7 years, and the reporting rates have been in-line with the frequency mentioned in the follitropin alfa/lutropin alfa (Pergoveris®) EU-SmPC. No additional pharmacovigilance activities and additional risk minimization activities have been conducted for this risk in the last 7 years. Furthermore, the Company considers that the risk is fully characterized and does not expect that any pharmacovigilance activities can further characterize the risk. Hence, the Company proposes to remove "Hypersensitivity reactions" as an important identified risk. The Company will continue to perform routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection activities).

Important Potential Risks:

Breast cancer

In the RMP version 1.0 (dated March 2006) approved by the EMA, "Reproductive system cancer" was proposed as an important identified risk by the Company. This risk was then reclassified as an important potential risk in the RMP version 2.0 (dated 18 August 2009) as no cases had been reported for follitropin alfa/lutropin alfa (Pergoveris®) and the terminology of this risk was changed to "Reproductive system cancer (including breast, ovarian and endometrial)". In the RMP version 3.0 (dated 14 February 2010), the risk was split into "Breast cancer", "Ovarian cancer" and "Endometrial cancer" (important potential risks).

Characterization of the risk:

The Company believes that the important potential risk of "Breast cancer" as fully characterized up to the DLP of the RMP version 5.3 (30 April 2019).

Overview of the important potential risk of breast cancer:

Safety concern		**Breast cancer**
Reason of initial addition of the risk		Proposed by the Company
Safety concern included in Pergoveris® EU-SmPC		• Section 4.3 "Contraindications" • Section 4.4 "Special Warnings and Precautions for Use"
	Cumulative reporting rate up to the DLP of RMP v5.3 i.e. 30 April 2019	0.0 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER period 20 October 2015 to 19 October 2018	0.0 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER, 25 June 2011 - 19 Oct 2015	0.0 per 100,000 treatment-cycles
Pharmacovigilance plan		**Routine pharmacovigilance activities:** Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) are considered sufficient for monitoring the safety concern of the medicinal product. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaires for safety concern: The Company has a follow-up questionnaire to monitor this risk Other forms of routine pharmacovigilance activities for safety concern: This risk is under close monitoring. **Additional pharmacovigilance activities:** None
Risk minimization measures		**Routine risk minimization activities:** Routine risk communication: Description of risk in women who undergo multiple treatment regimens for infertility (EU-SmPC Section 4.4 and PL Section 2). Routine risk minimization activities recommending specific clinical measures to address the risk: Instruction to clinically assess and rule out patients with pre-existing mammary carcinoma (EU-SmPC section 4.3 and PL section 2). Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine

Safety concern	Breast cancer
	Additional risk minimization activities: None

Evaluation for the removal of the risk:

This risk was added as a safety concern based on published epidemiological data which highlighted the risk of reproductive system cancers with gonadotropins (Jensen et al., 2007; Venn et al.,1999; Benshushan et al., 2001). There is some evidence that ovarian hormones play a crucial role at the development stages of the breast cancer and many clinically evident breast cancers remain sensitive to ovarian hormones. Both estradiol and progesterone seem to be involved in increasing breast cancer risk (Pike et al., 1993). Given that ovulation is an established breast cancer risk factor, the contributory role of gonadotropins by stimulating ovulation has been the subject of controversial publications. The potential mechanism has been linked to the fact that breast mitotic activity reaches its peak during the luteal phase of the menstrual cycle following ovulation (Pike MC et al., 1993) and that ovulation stimulating agents raise estradiol and progesterone levels (Sovino et al., 2002).

In a review, Russo et al. (2015) evaluated the risk of breast cancer and fertility drugs and found that the previous literature does not provide indisputable evidence for the association between ovarian stimulation and the risk of breast cancer. Additionally, after a median follow-up of 21 years following IVF treatment, van den Belt-Dusebout et al., (2016) reported that the incidence of breast cancer risk associated with IVF-treatment is not significantly different from that of the general population. Furthermore, Goldrat et al., (2015) studied 198 patients with a history of breast cancer and reported that pregnancy using ART in these women is feasible and does not seem to be detrimental to cancer outcome. Similarly, a study by Derks-Smeets et al., (2018) found no evidence for an association between ovarian stimulation for IVF and breast cancer risk in *BRCA1/2* mutation carriers.

Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) estimated that there will be 18.1 million cancer cases (17 million excluding non-melanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding non-melanoma skin cancer) in 2018 (Bray et al., 2018). Breast cancer is the most commonly diagnosed cancer and leading cause of cancer deaths among females, accounting for 11.6% of the total cases (Bray et al., 2018). Furthermore, the lifetime risk of breast cancer in the United Kingdom (UK) is one in nine females, with an annual incidence of <10 per 100,000 women aged <30 years, rising to 300 per 100,000 in women aged over 85 years (Hodgson et al., 2014). These epidemiologic data provide a reference for the frequency of reproductive system cancer in the general population. However, it might not be plausible to compare this reference of frequency of reproductive system cancer in the general population directly to the reporting rate computed for follitropin alfa/lutropin alfa (Pergoveris®) due to various limitations in the reporting e.g., under-reporting in the post-marketing setting.

In addition, Lambertini et al., (2016) published recommendations from physicians with expertise in the field of fertility preservation in cancer patients from several European countries. Experts were asked to present an up-to-date review of the literature published on these topics and the presentation of their own unpublished data was encouraged. On the basis of the data presented, as well as the expertise of the invited speakers, one of the recommendations was that “Ovarian

stimulating drugs with standard treatment protocols may be administered in subfertile/infertile women without increasing the risk of developing breast cancer" (considering evidence from prospective cohort studies; (Lambertini et al., 2016).

Cumulatively, no cases of breast cancer have been reported in the clinical trial and post-marketing setting up to the DLP of the RMP version 5.3 (30 April 2019). There has been no relevant change in the risk characteristics, over the last 7 years. In addition, this risk was under close monitoring over the last 7 years and has a follow-up questionnaire; nevertheless, no new relevant safety information has been revealed. Furthermore, the information in Section 4.3 "Contraindications" and Section 4.4 "Special Warnings and Precautions for Use" in the current EU-SmPC for follitropin alfa/lutropin alfa (Pergoveris®) adequately addresses this risk.

Risk minimization measures for the safety concern:

The Company considers that the current risk minimization measures for 'Breast cancer" are adequate; there has been no additional risk minimization activities for this safety concern for over the last 7 years. Furthermore, the product is contraindicated in patients with reproductive system carcinoma.

Conclusion:

From the time of inclusion of "Breast cancer" as an important potential risk for follitropin alfa/lutropin alfa (Pergoveris®), routine pharmacovigilance activities have been considered adequate for monitoring of the risk. The Company has closely monitored this risk over the last 7 years and no new relevant safety information has been revealed. Furthermore, no additional pharmacovigilance activities or additional risk minimization activities have been conducted for this risk. The Company considers the risk as fully characterized and does not expect that any pharmacovigilance activities can further characterize this risk. In addition, accumulated scientific and clinical data do not support the initial supposition, the impact to the individual has been shown to be less than anticipated resulting in the potential risk not being considered important. Thus, the Company proposes to remove "Breast cancer" as an important potential risk and as a closely monitored event for follitropin alfa/lutropin alfa (Pergoveris®). The Company will continue to perform routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection activities).

Ovarian Cancer

In the RMP version 1.0 (dated March 2006) approved by the EMA, "Reproductive system cancer" was proposed as an important identified risk by the Company. This risk was then reclassified to an important potential risk in the RMP version 2.0 (dated 18 August 2009) as no cases had been reported for follitropin alfa/lutropin alfa (Pergoveris®) and the terminology of this risk was changed to "Reproductive system cancer (including breast, ovarian and endometrial)". In the RMP version 3.0 (dated 14 February 2010), the risk was split into "Ovarian cancer", "Breast cancer", and "Endometrial cancer" (important potential risks).

Characterization of the risk:

The Company believes that the important potential risk of 'Ovarian cancer' as fully characterized up to the DLP of the RMP version 5.3 (30 April 2019).

Overview of the important potential risk of ovarian cancer:

Safety concern		**Ovarian Cancer**
Reason of initial addition of the risk		Proposed by the Company
Safety concern included in Pergoveris® EU-SmPC		• Section 4.3 "Contraindications" • Section 4.4 "Special Warnings and Precautions for Use"
	Cumulative reporting rate up to the DLP of RMP v5.3 i.e. 30 April 2019	0.0 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER period 20 October 2015 to 19 October 2018	0.0 per 100,000 treatmentcycles
	Cumulative reporting rate per PBRER, 25 June 2011 - 19 Oct 2015	0.0 per 100,000 treatment-cycles
Pharmacovigilance plan		**Routine pharmacovigilance activities:** Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) are considered sufficient for monitoring the safety concern of the medicinal product. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaires for safety concern: The Company has a follow-up questionnaire to monitor this risk Other forms of routine pharmacovigilance activities for safety concern: This risk is under close monitoring **Additional pharmacovigilance activities:** None
Risk minimization measures		**Routine risk minimization activities:** Routine risk communication: Description of risk in women who undergo multiple treatment regimens for infertility (EU-SmPC Section 4.4 and PL Section 2). Routine risk minimization activities recommending specific clinical measures to address the risk: Instruction to clinically assess and rule out patients with pre-existing ovarian carcinoma (EU-SmPC section 4.3 and PL section 2). Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine

Safety concern	Ovarian Cancer
	Additional risk minimization activities: None

Evaluation for the removal of the risk:

Ovarian cancer is a common gynecologic malignancy which significantly threatens women's lives. It has high morbidity and mortality rates among cancers of the reproductive system. This risk was added as a safety concern based on the published epidemiological data which highlighted the risk of reproductive system cancers with gonadotropins (Jensen et al., 2007; Venn et al.,1999; Benshushan et al., 2001)

There is little information in the published literature in relation to the use of follitropin alfa/lutropin alfa (Pergoveris®) in women with severe FSH and LH deficiency and ovarian cancer. Siristatidis et al., (2012) conducted a systemic review and meta-analysis and reported that ovarian stimulation for IVF does not increase ovarian or endometrial cancers. Diergaarde et al., (2014) evaluated the use of fertility drugs and risk of ovarian cancer and concluded that fertility drug use does not significantly contribute to the risk of ovarian cancer. It was further reported that establishing the relationship between fertility drug use and ovarian cancer risk is complex due to the fact that infertility itself increases the risk of ovarian cancer. Furthermore, Gronwald et al., (2016) studied matched case-control of 941 pairs of *BRCA1* or *BRCA2* mutation carriers with and without a diagnosis of ovarian cancer. The authors' findings suggested that treatment for infertility does not significantly increase the risk of ovarian cancer among women with a *BRCA* mutation.

As per GLOBOCAN estimates, 0.29 million new patients are newly diagnosed in 2018 and approximately 0.18 million people die from this cancer (Bray et al., 2018). This international epidemiologic data is not directly comparable to the reporting rate computed for follitropin alfa/lutropin alfa (Pergoveris®), but they do provide a reference for the frequency of ovarian cancer in the general population.

Cumulatively, no cases of "Ovarian cancer" have been reported in the post-marketing setting up to the DLP of the RMP version 5.3 (30 April 2019). There has been no relevant change in the risk characteristics, over the last 7 years. The Company has closely monitored this risk over the last 7 years and has a follow-up questionnaire; nevertheless, no new relevant safety information has been revealed. Furthermore, the information in Section 4.3 "Contraindications" and Section 4.4 "Special Warnings and Precautions for Use" in the current EU-SmPC for follitropin alfa/lutropin alfa (Pergoveris®) adequately addresses this risk.

Risk minimization measures for the safety concern:

The Company considers that the current risk minimization measures for "Ovarian cancer" are adequate; there has been no additional risk minimization activities for this safety concern for over 7 years. Furthermore, the product is contraindicated in patients with reproductive system carcinoma.

Conclusion:

From the time of inclusion of "Ovarian cancer" as an important potential risk for follitropin alfa/lutropin alfa (Pergoveris®), routine pharmacovigilance activities have been considered adequate for monitoring of the risk. The Company has closely monitored this risk over the last 7 years and no new safety information has been revealed. Furthermore, no additional pharmacovigilance activities or additional risk minimization activities have been conducted for this risk. The Company considers the risk as fully characterized and does not expect that any pharmacovigilance activities can further characterize this risk. In addition, accumulated scientific and clinical data do not support the initial supposition, the impact to the individual has been shown to be less than anticipated resulting in the potential risk not being considered important. Thus, the Company proposes to remove "Ovarian cancer" as an important potential risk and as a closely monitored event for follitropin alfa, lutropin alfa / Pergoveris®. The Company will continue to perform routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection activities).

Endometrial cancer

In the RMP version 1.0 (dated March 2006) approved by the EMA, "Reproductive system cancer" was proposed as an important identified risk by the Company. This risk was then reclassified to an important potential risk in the RMP version 2.0 (dated 18 August 2009) as no cases had been reported for follitropin alfa/lutropin alfa (Pergoveris®) and the terminology of this risk was changed to "Reproductive system cancer (including breast, ovarian, and endometrial)". In the RMP version 3.0 (dated 14 February 2010), the risk was split into "Ovarian cancer", "Breast cancer" and "Endometrial cancer" (important potential risks).

Characterization of the risk:

The Company believes that the important potential risk of 'Endometrial cancer' as fully characterized up to the DLP of the RMP version 5.3 (30 April 2019).

Overview of the important potential risk of Endometrial Cancer:

Safety concern		**Endometrial Cancer**
Reason of initial addition of the risk		Proposed by the Company
Safety concern included in Pergoveris® EU-SmPC		• Section 4.3 "Contraindications" • Section 4.4 "Special Warnings and Precautions for Use"
	Cumulative reporting rate up to the DLP of RMP v5.3 i.e. 30 April 2019	0.0 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER period 20 October 2015 to 19 October 2018	0.0 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER, 25 June 2011 - 19 Oct 2015	0.0 per 100,000 treatment-cycles
Pharmacovigilance plan		**Routine pharmacovigilance activities:**

Safety concern	Endometrial Cancer
	Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) are considered sufficient for monitoring the safety concern of the medicinal product. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaires for safety concern: The Company has a follow-up questionnaire to monitor this risk. Other forms of routine pharmacovigilance activities for safety concern: This risk is under close monitoring **Additional pharmacovigilance activities:** None
Risk minimization measures	**Routine risk minimization activities:** Routine risk communication: Description of risk in women who undergo multiple treatment regimens for infertility (EU-SmPC Section 4.4 and PL Section 2). Routine risk minimization activities recommending specific clinical measures to address the risk: Instruction to clinically assess and rule out patients with pre-existing uterine carcinoma (EU-SmPC section 4.3 and PL section 2). Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine **Additional risk minimization activities:** None

Evaluation for the removal of the risk:

There is little information in the published literature in relation to the use of follitropin alfa/lutropin alfa (Pergoveris®) in women with severe FSH and LH deficiency and endometrial cancer.

Siristatidis et al., (2012) conducted a systemic review and meta-analysis and reported that ovarian stimulation for IVF does not increase ovarian or endometrial cancers. Similarly, a meta-analysis conducted by Saso et al., (2015) showed no link between fertility drugs and uterine cancers post-treatment. In addition, a cohort study by Luke et al., (2015) did not find any association between ART and risks of ovarian or uterine cancer.

Cumulatively, no cases of “Endometrial cancer” have been reported in the clinical trial and post-marketing setting up to the DLP of the RMP version 5.3 (30 April 2019). There has been no relevant change in the risk characteristics, over the last 7 years. The Company has closely monitored this risk over the last 7 years and has a follow-up questionnaire; nevertheless, no new relevant safety information has been revealed. Furthermore, the information in Section 4.3 “Contraindications” and Section 4.4 “Special Warnings and Precautions for Use” in the current EU-SmPC for follitropin alfa/lutropin alfa (Pergoveris®) adequately addresses this risk.

Risk minimization measures for the safety concern:

The Company considers the current risk minimization measures for "Endometrial cancer" are adequate; there has been no additional risk minimization activities for this safety concern for over 7 years. Furthermore, the product is contraindicated in patients with reproductive system carcinoma.

Conclusion:

From the time of inclusion of "Endometrial cancer" as an important potential risk for follitropin alfa/lutropin alfa (Pergoveris®), routine pharmacovigilance activities have been considered adequate for monitoring the risk. Furthermore, no additional pharmacovigilance activities or additional risk minimization activities have been conducted for this risk. The Company has closely monitored this risk over the last 7 years and no new safety information has been revealed. The Company considers the risk as fully characterized and does not expect that any pharmacovigilance activities can further characterize this risk. In addition, accumulated scientific and clinical data do not support the initial supposition, the impact to the individual has been shown to be less than anticipated resulting in the potential risk not being considered important. Thus, the Company proposes to remove "Endometrial cancer" as an important potential risk and as a closely monitored event for follitropin alfa/lutropin alfa (Pergoveris®). The Company will continue to perform routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection activities).

Congenital anomalies

"Congenital anomalies" was proposed as an important potential risk for follitropin alfa/lutropin alfa (Pergoveris®) by the Company in the RMP version 2.0 (dated 18 August 2009)/ RMP version 3.0 (dated 14 February 2010, EMA approved). Approximately 2-3% of live births reportedly have a major congenital abnormality. This percentage is believed to be higher in infertile couples because of age (couples requiring ART being usually older) and other factors that lead to infertility (infection, hormonal imbalance, sperm abnormalities etc.). The exact level of increased risk or the mechanisms causing these congenital anomalies is not known. It was also found that infertile couples whether they conceived with ART or conceived spontaneously had an increased risk of having children with congenital anomalies.

Characterization of the risk:

The Company believes that the important potential risk of "Congenital anomalies" as fully characterized up to the DLP of the RMP version 5.3 (30 April 2019).

Safety concern		**Congenital abnormalities**
Reason of initial addition of the risk		Proposed by the Company
Safety concern included in Pergoveris® Summary of Product Characteristics (EU-SmPC)		• Section 4.4 "Special Warnings and Precautions for Use"
	Cumulative reporting rate up to the DLP of RMP v5.3 i.e. 30 April 2019	0.0 per 100,000 treatment-cycles

Safety concern		**Congenital abnormalities**
	Cumulative reporting rate per PBRER period 20 October 2015 to 19 October 2018	0.0 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER, 25 June 2011 - 19 Oct 2015	0.0 per 100,000 treatment-cycles
Pharmacovigilance plan		**Routine pharmacovigilance activities:** Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) are considered sufficient for monitoring the safety concern of the medicinal product. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaires for safety concern: The Company has a follow-up questionnaire to monitor risk Other forms of routine pharmacovigilance activities for safety concern: This risk is under close monitoring **Additional pharmacovigilance activities:** None
Risk minimization measures		**Routine risk minimization activities:** Routine risk communication: Description of prevalence of risk of congenital abnormalities after ART (SmPC Section 4.4). Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine Additional risk minimization activities: None

Evaluation for the removal of the risk:

Congenital anomalies can be defined as structural or functional anomalies (for example, metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth, or may only be detected later in infancy, such as hearing defects (WHO 2016). Most congenital anomalies are the result of genetic abnormalities, whether acquired by inheritance or mutation. In some cases, the genetic mutation could be associated to an external factor like an infection or drug, but in many cases no identifiable cause can be found, hence classed as spontaneous chromosomal aberrations. Other teratogenic factors can cause abnormalities by interfering with the fetal developmental processes leading to morphogenetic errors. The type and severity of defect is related to the time,

type, strength and length of the exposure to the teratogenic factor. Infertility is a risk factor for congenital anomaly (Zhu et al., 2006). Factors like mother's age or multiple pregnancies are risk factors for fetal or neonatal anomalies (Bergh et al.,1999; Westergaard et al., 1999).

There is little information in the published literatures in relation to the use of follitropin alfa/lutropin alfa (Pergoveris®) in women with severe FSH and LH deficiency and its potential relation to congenital anomalies. The prevalence of congenital anomaly cases (including live births, fetal deaths more than 20 weeks and terminations of pregnancy for fetal anomaly) per 1,000 births in the general population according to European Concerted Action on Congenital Anomalies and Twins (EUROCAT) data is 26.9 (Boyle et al., 2018). Of these, 77.0% were live births surviving infancy. This international epidemiologic data is not directly comparable to the reporting rate computed for follitropin alfa/lutropin alfa (Pergoveris®), but they do provide a reference for the frequency of these events in the general population.

Cumulatively, no cases of "Congenital anomalies" have been reported in the post-marketing setting up to the DLP of the RMP version 5.3 (30 April 2019). The Company has closely monitored this risk over the last 7 years and has a follow-up questionnaire for monitoring; nevertheless, no new relevant safety information has been revealed. Furthermore, the information in Section 4.4 "Special Warnings and Precautions for Use" in the current EU-SmPC for follitropin alfa/lutropin alfa (Pergoveris®) adequately addresses this risk. There has been no relevant change in the risk characteristics of "Congenital anomaly" over the last 7 years, including the frequency of this risk.

Risk minimization measures for the safety concern:

The Company considers the current risk minimization measures for "Congenital anomalies" are adequate. There have been no additional risk minimization activities for this safety concern for over 7 years. Furthermore, the information in Section 4.4 "Special Warnings and Precautions for Use" in the current EU-SmPC for follitropin alfa/lutropin alfa (Pergoveris®) adequately addresses this risk.

There are several preventive measures that can be taken to reduce congenital anomalies such as: clinical care of high risk women (with chronic disease status like diabetes and epilepsy), maternal infection control, avoidance of known teratogenic agents, cessation of maternal smoking, alcohol consumption and recreational drugs, pre-marketing drug testing, maternal nutritional considerations, reduction of exposure to environmental pollutants and genetic counselling for high risk families (EUROCAT Special Report 2012).

Conclusion

From the time of inclusion of "Congenital anomalies" as an important potential risk for follitropin alfa/lutropin alfa (Pergoveris®), routine pharmacovigilance activities have been considered adequate for monitoring of the risk. The Company has closely monitored this risk over the last 7 years and no new safety information has been revealed. Furthermore, no additional pharmacovigilance activities and additional risk minimization activities have been conducted for this risk. The Company considers the risk as fully characterized and does not expect that any pharmacovigilance activities can further characterize this risk. Thus, the Company proposes to remove "Congenital anomalies" as an important potential risk and as a closely monitored event for

follitropin alfa, lutropin alfa / Pergoveris®. The Company will continue to perform routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection activities).

Malignant Melanoma:

The initial inclusion of "Malignant melanoma" as an important potential risk for follitropin alfa, lutropin alfa / Pergoveris® was done as per the recommendation of the Committee for Medicinal Products for Human Use (CHMP) (EMA/924333/2011) in the RMP version 4.2 (DLP 19 October 2015).

Speculations on a direct or indirect relationship between fertility drugs and malignant melanoma have been made based on the possible increased risk in conditions where high levels of reproductive hormones exist (i.e. pregnancy) or with the use of hormonal treatment (oral contraceptives and hormonal replacement therapy) and on in-vitro findings.

Characterization of the risk:

The Company believes that the important potential risk of "Malignant Melanoma" as fully characterized up to the DLP of the RMP version 5.3 (30 April 2019).

Overview of the important potential risk of malignant melanoma

Safety concern		**Malignant melanoma**
Reason of initial addition of the risk		As per recommendation of the CHMP (EMA/924333/2011)
Safety concern included in Pergoveris® EU-SmPC		• None
	Cumulative reporting rate up to the DLP of RMP v5.3 i.e. 30 April 2019	0.1 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER period 20 October 2015 to 19 October 2018	0.2 per 100,000 treatment-cycles
	Cumulative reporting rate per PBRER, 25 June 2011 - 19 Oct 2015	0.0 per 100,000 treatment-cycles
Pharmacovigilance plan		**Routine pharmacovigilance activities:** Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) are considered sufficient for monitoring safety concern of the medicinal product. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaires for safety concern: The Company has a follow-up questionnaire to monitor risk Other forms of routine pharmacovigilance activities for safety concern: This risk is under close monitoring **Additional pharmacovigilance activities:** None
Risk minimization measures		**Routine risk minimization activities:** Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine **Additional risk minimization activities:** None

Evaluation for the removal of the risk:

There is little information in the published literatures on the use of follitropin alfa/lutropin alfa (Pergoveris®) in women with severe FSH and LH deficiency and its relationship to malignant melanoma. As per GLOBOCAN estimates, 0.29 million new patients are newly diagnosed in 2018 with melanoma of skin and approximately 0.06 million people die from this cancer (Bray et al., 2018). This international epidemiologic data is not directly comparable to the reporting rate computed for follitropin alfa/lutropin alfa (Pergoveris®), but they do provide a reference for the frequency of malignant melanoma in the general population.

In the post-marketing experience, only one case of "Malignant melanoma" has been received up to the DLP of the RMP (30 April 2019). The cumulative reporting rate shows that "Malignant melanoma" is reported very rarely, i.e., <1/10,000.

From the first Marketing Authorization (MA) date of the product (25 June 2007), no new clinical data has been received to support the initial inclusion of "Malignant melanoma" as an important potential risk for follitropin alfa/lutropin alfa (Pergoveris®). In December 2010, de novo and recurrent malignant melanoma was placed under close monitoring by the Company as a precautionary measure after receipt of two recurrent malignant melanoma cases. The Company has a follow-up questionnaire for monitoring "Melanoma, de novo and recurrent". There has been no relevant change in the risk characteristics of "Malignant melanoma" over the last 7 years, including the frequency of this risk.

Conclusion:

From the time of inclusion of "Malignant melanoma" as an important potential risk for follitropin alfa/lutropin alfa (Pergoveris®), routine pharmacovigilance activities have been considered adequate for monitoring of the risk. Furthermore, no additional pharmacovigilance activities or additional risk minimization activities has been conducted for this risk. The Company has closely monitored this risk since 2010 and no new safety information has been revealed. The Company considers the risk as fully characterized and does not expect that any pharmacovigilance activities can further characterize this risk. In addition, accumulated scientific and clinical data do not support the initial supposition, the impact to the individual has been shown to be less than anticipated resulting in the potential risk not being considered important. Thus, the Company proposes to remove "Malignant melanoma" as an important potential risk and as a closely monitored event for follitropin alfa/lutropin alfa (Pergoveris®). The Company will continue to perform routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection activities).

Missing Information

Premenopausal women with severe LH and FSH deficiency older than 42 years

The Company has evaluated the classification of the missing information "Premenopausal women with severe LH and FSH deficiency older than 42 years" and proposes to remove it from the summary of safety concerns.

The current analysis was conducted based on the information available to the Company up to the 12 September 2019 i.e. clinical trial data and post-marketing data including literature review.

Clinical trial data:

There are no Company sponsored clinical studies data for the use of Pergoveris® in woman older than 42 years age.

Post-marketing:

For post-marketing data analysis, a review of relevant literature, post-marketing studies and ICSRs in the Company's safety database was performed.

Company's Safety Database:

A search was conducted in the Company safety database Adverse Reaction Information System Global (ARISg), Medical Dictionary for Regulatory Activities (MedDRA version 21.0), using medical history and the specified PTs "Blood follicle stimulating hormone abnormal", "Blood follicle stimulating hormone decreased", "Blood luteinising hormone abnormal", and "Blood luteinising hormone decreased", for women over 42 years of age.

Cumulatively up to DLP of 30 April 2019, no ICSRs have been received for this missing information.

Post-marketing safety studies:

One post-marketing study for Pergoveris® in relation to women over 42 years has been conducted by the Company.

Study	Details
EMR200061-507	A Korean Post-marketing surveillance (PMS) for Pergoveris® women with severe deficiency of LH and FSH defined by less than 1.2 IU/L of endogenous serum LH.
Age Group	600 subjects in the safety population 67 subjects (11.2%) were aged 40 to 49 years
Safety findings	The reporting pattern of adverse events after Pergoveris® treatment in this study was similar to the known safety profile of the product. It was concluded that there were no new safety findings from the study that impact the benefit-risk assessment of the product.

Literature:

The Company has reviewed the literature from the Medline databases using the following criteria up to 12 September 2019: The search is directed to clinical studies or meta-analyses comprising efficacy and safety data on Gonal-f®/r-hFSH, Luveris®/r-hLH, Pergoveris®/r-hFSH+r-hLH including ART procedures in female patients >38 years. The search retrieved 128 articles, of which 110 articles were potentially relevant.

Additionally, published literature available to the Company was reviewed.

Screening of the literature did not reveal any new relevant safety findings for Pergoveris®/r-hFSH+r-hLH or ART (outside the known safety profile) in female patients older than 42 years, including the use in premenopausal women with severe LH and FSH deficiency who have been treated for infertility (e.g. Blumenauer et al., 2018; Seng et al., 2005; Yovich et al., 2018).

Some of the literature articles give credence to the occurrence of known age-related risks such as increased rate of miscarriage (Liu et al., 2012; Seng et al., 2005; Blumenauer et al., 2018; Pezeshki et al., 2000; Yovich et al., 2018), congenital anomalies (Liu et al., 2012; Bergh et al.,1999), antenatal and perinatal complications in mother and offspring (Cleary-Goldman et.al., 2005; Liu et al., 2012; Seng et al., 2005), and decreased clinical pregnancy rates (Osaikhuwuomwan et al., 2018; Xu et al., 2018; Liu et al., 2012; Seng et al., 2005; Blumenauer et al., 2018), which are not related to the product but infertility and patient characteristics. No specific product related safety findings were mentioned.

Conclusion:

Considering no ICSRs in the Company's safety database on the use of Pergoveris®, no new relevant safety concerns were identified for the subpopulation of "premenopausal women with severe LH and FSH deficiency older than 42 years". In this context and outside the known risks associated with advanced maternal age (such as miscarriage), the safety profile in this subpopulation is considered to be similar to the product generally. The use of Pergoveris® as a treatment for infertility at this higher age would likely be limited; however, the product is typically used in association with specialized infertility treatment clinics where appropriate clinician - patient interaction and clinical management can minimize some risks related to advanced maternal age.

Routine pharmacovigilance activities have been considered adequate for monitoring of safety for the use of Pergoveris® in "Premenopausal women with severe LH and FSH deficiency older than 42 years" since 2007, and no additional risk minimization measures have been in place for this missing information. There is no reasonable expectation that the existing or future pharmacovigilance activities could further characterize this missing information. Hence, the Company proposes to remove this missing information from the list of safety concerns.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2 Presentation of the Missing Information

Not applicable.

Part II: Module SVIII Summary of the Safety Concerns

There are no safety concerns for the product.

Table 3 Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Part III: Pharmacovigilance Plan (including Post-Authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities (including adverse reaction reporting, literature surveillance and signal detection) are considered sufficient for monitoring the safety concerns of the medicinal product.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for Safety Concerns:

None

Other forms of routine Pharmacovigilance Activities for Safety Concerns:

None.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

No studies are ongoing or planned as a part of additional pharmacovigilance activities for Pergoveris®.

Part IV: Plans for Post-authorization Efficacy Studies

There are no post-authorization efficacy studies ongoing or planned for Pergoveris®.

Part V: Risk Minimization Plan (including Evaluation of the Effectiveness of Risk Minimization Activities)

V.1 Routine Risk Minimization Measures

Pergoveris® is a prescription only medicine.

V.2 Additional Risk Minimization Measures

No additional risk minimization activity for Pergoveris®.

V.3 Summary of Risk Minimization Measures

Pergoveris® is a prescription only medicine. There are no additional pharmacovigilance and additional risk minimization activities.

Part VI: Summary of the Risk Management Plan

Summary of the Risk Management Plan for follitropin alfa/lutropin alfa (Pergoveris®)

This is a summary of the Risk Management Plan (RMP) for Pergoveris®. The RMP details important risks of Pergoveris®, how these risks can be minimized, and how more information will be obtained about Pergoveris® risks and uncertainties (missing information).

Pergoveris® Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Pergoveris® should be used.

This summary of the RMP for Pergoveris® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Pergoveris® RMP.

I. The Medicine and What it is used for

In the European Union (EU), Pergoveris® is indicated for the stimulation of follicular development in adult women with severe LH and FSH deficiency.

Pergoveris® contains follitropin alfa and lutropin alfa as the active substance and it is given by subcutaneous route of administration.

Further information about the evaluation of Pergoveris®'s benefits can be found in Pergoveris®'s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to the product's EPAR summary landing page.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Pergoveris® together with measures to minimize such risks and the proposed studies for learning more about Pergoveris®'s risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine Risk Minimization Measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine Pharmacovigilance Activities.

If important information that may affect the safe use of Pergoveris® is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Pergoveris® are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Pergoveris®. Potential risks are concerns for which an association with the use of this medicine is possible, based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

There are no important identified or potential risks or missing information.

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

II.B Summary of Important Risks

There are no important identified or important potential risks or missing information for the product.

II.C Post-authorization Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorization.

There are no studies which are conditions of the marketing authorization or specific obligation of Pergoveris®.

II.C.2 Other Studies in the Post-Authorization Development Plan

There are no studies required for Pergoveris®.

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Part VII Annexes

Annex 1 EudraVigilance Interface (available in electronic format only)

Annex 2 Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Not applicable

Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Not applicable

Annex 4 Specific Adverse Drug Reaction Follow-up Forms

Not applicable

Annex 5 Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable

Annex 6 Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable

Annex 7 Other Supporting Data (including Referenced Material) (see References)

Annex 8 Summary of Changes to the Risk Management Plan over Time