1. NAME OF THE MEDICINAL PRODUCT

Ovitrelle 250 micrograms/0.5 mL solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 250 micrograms choriogonadotropin alfa* (equivalent to approximately 6,500 IU) in 0.5 mL solution.

* recombinant human chorionic gonadotropin, r-hCG produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear, colourless to slightly yellow solution.
The pH of the solution is 7.0 ± 0.3, its osmolality 250-400 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovitrelle is indicated in the treatment of

- Adult women undergoing superovulation prior to assisted reproductive technologies (ART) such as in *vitro* fertilisation (IVF): Ovitrelle is administered to trigger final follicular maturation and luteinisation after stimulation of follicular growth,

- Anovulatory or oligo-ovulatory adult women: Ovitrelle is administered to trigger ovulation and luteinisation in anovulatory or oligo-ovulatory women after stimulation of follicular growth.

4.2 Posology and method of administration

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

Posology

The maximum dose is 250 micrograms. The following dose regimen should be used:

- Women undergoing superovulation prior to assisted reproductive technologies (ART) such as *in vitro* fertilisation (IVF):

  One pre-filled syringe of Ovitrelle (250 micrograms) is administered 24 to 48 hours after the last administration of a follicle stimulating hormone (FSH) or human menopausal gonadotropin (hMG) preparation, i.e. when optimal stimulation of follicular growth is achieved.

- Anovulatory or oligo-ovulatory women:

  One pre-filled syringe of Ovitrelle (250 micrograms) is administered 24 to 48 hours after optimal stimulation of follicular growth is achieved. The patient is recommended to have coitus on the day of, and the day after, Ovitrelle injection.

Special populations

Renal or hepatic impairment
Safety, efficacy and pharmacokinetics of Ovitrelle in patients with renal or hepatic impairment have not been established.

Paediatric population
There is no relevant use of Ovitrelle in the paediatric population.

Method of administration

For subcutaneous use. Self-administration of Ovitrelle should only be performed by patients who are adequately trained and have access to expert advice.
Ovitrelle is for single use only.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Tumours of the hypothalamus or pituitary gland
- Ovarian enlargement or cyst unrelated to polycystic ovarian syndrome
- Gynaecological haemorrhages of unknown aetiology
- Ovarian, uterine or mammary carcinoma
- Active thromboembolic disorders

Ovitrelle must not be used in conditions when an effective response cannot be obtained, such as
- primary ovarian failure
- malformations of sexual organs incompatible with pregnancy
- fibroid tumours of the uterus incompatible with pregnancy
- postmenopausal women

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and pituitary or hypothalamic tumours, and appropriate specific treatment given.

There is no clinical experience with Ovitrelle in the treatment of other conditions (such as corpus luteum insufficiency or male conditions); therefore, Ovitrelle is not indicated in these conditions.

Ovarian hyperstimulation syndrome (OHSS)

A certain degree of ovarian enlargement is an expected effect of controlled ovarian stimulation. It is more commonly seen in women with polycystic ovarian syndrome and usually regresses without treatment.

In distinction to uncomplicated ovarian enlargement, OHSS is a condition that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.

Mild manifestations of OHSS may include abdominal pain, abdominal discomfort and distension, and enlarged ovaries. Moderate OHSS may additionally present with nausea, vomiting, ultrasound evidence of ascites and marked ovarian enlargement.

Severe OHSS further includes symptoms such as severe ovarian enlargement, weight gain, dyspnoea or oliguria. Clinical evaluation may reveal signs such as hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, pleural effusions, or acute pulmonary distress. Very rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events, such as pulmonary embolism, ischaemic stroke or myocardial infarction.

Independent risk factors for developing OHSS include young age, lean body mass, polycystic ovarian syndrome, higher doses of exogenous gonadotropins, high absolute or rapidly rising serum estradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in ART cycles.

Adherence to recommended Ovitrelle dosage and regimen of administration can minimise the risk of ovarian hyperstimulation. Monitoring of stimulation cycles by ultrasound scans as well as estradiol measurements are recommended to early identify risk factors.

There is evidence to suggest that hCG plays a key role in triggering OHSS and that the syndrome may be more severe and more protracted if pregnancy occurs. Therefore, if signs of ovarian hyperstimulation occur, it is recommended that hCG be withheld and the patient be advised to refrain from coitus or use barrier contraceptive methods for at least 4 days.

As OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event, patients should be followed for at least two weeks after hCG administration.

Mild or moderate OHSS usually resolves spontaneously. If severe OHSS occurs, it is recommended that gonadotropin treatment be stopped and that the patient be hospitalised and appropriate therapy be started.

Multiple pregnancy

In patients undergoing induction of ovulation, the incidence of multiple pregnancy and births is increased compared with natural conception. The majority of multiple conceptions are twins. Multiple pregnancies, especially high order, carry an increased risk of adverse maternal and perinatal outcomes.

To minimise the risk of higher order multiple pregnancy, careful monitoring of ovarian response is recommended. In patients undergoing ART procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient age.

Pregnancy loss

The incidence of pregnancy loss by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than following natural conception.

Ectopic pregnancy

Women with a history of tubal disease are at increased risk for ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. The prevalence of ectopic pregnancy after ART in this population was reported to be higher than in the general population.

Congenital malformations

The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and the higher incidence of multiple pregnancies.

Thromboembolic events

In women with recent thromboembolic disease or women with generally recognised risk factors for thromboembolic events, such as personal or family history, treatment with gonadotropins may further increase the risk for aggravation or occurrence of such events. In these women, the benefits of gonadotropin administration need to be weighed against the risks. It should be noted, however, that pregnancy itself as well as OHSS also carry an increased risk of thromboembolic events.

Reproductive system neoplasms

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple treatment regimens for infertility. It is not yet established whether or not treatment with gonadotropins increases the risk of these tumours in infertile women.

Interference with serum or urinary testing

Following administration, Ovitrelle may interfere for up to ten days with the immunological determination of serum or urinary hCG, potentially leading to a false positive pregnancy test. Patients should be made aware of this.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies with Ovitrelle and other medicinal products have been performed; however, no clinically significant medicinal product interactions have been reported during hCG therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no indication for the use of Ovitrelle during pregnancy. Data on a limited number of exposed pregnancies indicate no increased risks of malformation or foeto/neonatal toxicity. No reproduction studies with choriogonadotropin alfa in animals were performed (see section 5.3). The potential risk for humans is unknown.

Breast-feeding

Ovitrelle is not indicated during breastfeeding. There are no data on the excretion of choriogonadotropin alfa in milk.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

In comparative trials with different doses of Ovitrelle, OHSS was found to be associated with Ovitrelle in a dose-related fashion. OHSS was observed in approximately 4% of patients treated with Ovitrelle. Severe OHSS was reported in less than 0.5% of patients (see section 4.4).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Immune system disorders
Very rare: Mild to severe hypersensitivity reactions including rash, anaphylactic reactions and shock

Nervous system disorders
Common: Headache

Vascular disorders
Very rare: Thromboembolism (both in association with and separate from OHSS)

Gastrointestinal disorders
Common: Abdominal pain, abdominal distension, nausea, vomiting
Uncommon: Abdominal discomfort, diarrhoea

Reproductive system and breast disorders
Common: Mild or moderate OHSS
Uncommon: Severe OHSS

General disorders and administration site conditions
Common: Injection site reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

The effects of an overdose of Ovitrelle are unknown. Nevertheless, there is a possibility that OHSS may result from an overdose of Ovitrelle (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, gonadotropins, ATC code: G03GA08

Mechanism of action

Ovitrelle is a medicinal product of choriogonadotropin alfa produced by recombinant DNA techniques. It shares the amino acid sequence with urinary hCG. Chorionic gonadotropin binds on the ovarian theca (and granulosa) cells to a transmembrane receptor shared with the luteinising hormone, the LH/CG receptor.

Pharmacodynamic effects

The principal pharmacodynamic activity in women is oocyte meiosis resumption, follicular rupture (ovulation), corpus luteum formation and production of progesterone and estradiol by the corpus luteum.

In women, chorionic gonadotropin acts as a surrogate luteinising hormone surge that triggers ovulation.

Ovitrelle is used to trigger final follicular maturation and early luteinisation after use of medicinal products for stimulation of follicular growth.

Clinical efficacy and safety

In comparative clinical trials, administration of a dose of 250 micrograms of Ovitrelle was as effective as 5,000 IU and 10,000 IU of urinary hCG in inducing final follicular maturation and early luteinisation in assisted reproductive technologies, and as effective as 5,000 IU of urinary hCG in ovulation induction.

So far, there are no signs of antibody development in humans to Ovitrelle. Repeated exposure to Ovitrelle was investigated in male patients only. Clinical investigation in women for the indication of ART and anovulation was limited to one treatment cycle.

5.2 Pharmacokinetic properties

Following intravenous administration, choriogonadotropin alfa is distributed to the extracellular fluid space with a distribution half-life of around 4.5 hours. The steady-state volume of distribution and the total clearance are 6 L and 0.2 L/h, respectively. There are no indications that choriogonadotropin alfa is metabolised and excreted differently than endogenous hCG.

Following subcutaneous administration, choriogonadotropin alfa is eliminated from the body with a terminal half-life of about 30 hours, and the absolute bioavailability is about 40%.

A comparative study between the freeze-dried and the liquid formulation showed bioequivalence between the two formulations.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Studies on carcinogenic potential were not performed. This is justified, given the proteinous nature of the active substance and the negative outcome of the genotoxicity testing.

Studies on reproduction were not performed in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Methionine
Poloxamer 188
Phosphoric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.
After opening, the medicinal product should be used immediately. However, the in-use stability has been demonstrated for 24 hours at + 2°C to 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Store in the original package. Within its shelf-life, the solution may be stored at or below 25°C for up to 30 days without being refrigerated again during this period. It must be discarded if not used after these 30 days.

6.5 Nature and contents of container

0.5 mL of solution in a pre-filled syringe (type I glass) with a plunger stopper (halobutyl rubber) and plunger (plastic), and with a needle for injection (stainless) – pack of 1.

6.6 Special precautions for disposal and other handling

Only clear solution without particles should be used.
For single use only.

Self-administration of Ovitrelle should only be performed by patients who are adequately trained and have access to expert advice.

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

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

10 DATE OF REVISION OF THE TEXT

Oct-2021