

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## 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  $7.0 \pm 0.3$ , 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 techniques 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 techniques 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 due to reasons other than polycystic ovarian disease
- Gynaecological haemorrhages of unknown aetiology
- Ovarian, uterine or mammary carcinoma
- Extrauterine pregnancy in the previous 3 months
- Active thromboembolic disorders
- 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**

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)

Patients undergoing ovarian stimulation are at an increased risk of developing OHSS due to multiple follicular development.

Ovarian hyperstimulation syndrome may become a serious medical event characterised by large ovarian cysts, which are prone to rupture, weight gain, dyspnoea, oliguria or the presence of ascites within a clinical picture of circulatory dysfunction. Severe OHSS could be complicated in rare cases by haemoperitoneum, acute pulmonary distress, ovarian torsion, and thromboembolism.

To minimise the risk of OHSS, ultrasonographic assessments of follicular development and/or determination of serum estradiol levels should be performed prior to treatment and at regular intervals during treatment. In anovulation, the risk of OHSS is increased by a serum estradiol level > 1500 pg/mL (5400 pmol/L) and more than 3 follicles of 14 mm or more in diameter. In assisted reproductive techniques, there is an increased risk of OHSS with a serum estradiol > 3,000 pg/mL (11,000 pmol/L) and 18 or more follicles of 11 mm or more in diameter.

OHSS due to excessive ovarian response can be avoided by withholding hCG administration. Therefore, if signs of ovarian hyperstimulation occur such as serum estradiol level > 5,500 pg/mL (20,000 pmol/L) and/or when there are 30 or more follicles in total, it is recommended to withhold

hCG administration and the patient be advised to refrain from coitus or to use barrier contraceptive methods for at least 4 days.

#### Multiple pregnancy

In patients undergoing induction of ovulation, the incidence of multiple pregnancy and births (mostly twins) is increased compared with natural conception. The risk of multiple pregnancy following assisted reproductive techniques is related to the number of embryos replaced.

Adherence to recommended Ovitrelle dose, regimen of administration and careful monitoring of therapy will minimise the risk of OHSS and multiple pregnancy.

#### Miscarriage

The rate of miscarriage, in both anovulatory patients and women undergoing assisted reproductive techniques, is higher than that found in the normal population but comparable with the rates observed in women with other fertility problems.

#### Ectopic pregnancy

Since infertile women undergoing ART, and particularly IVF, often have tubal abnormalities, the incidence of ectopic pregnancies might be increased. It is important to have early ultrasound confirmation that a pregnancy is intrauterine, and to exclude the possibility of extrauterine pregnancy.

#### Congenital malformations

The incidence 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 or ongoing 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, such as pulmonary embolism, ischaemic stroke or myocardial infarction.

#### 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.

#### Other information

During Ovitrelle therapy, a minor thyroid stimulation is possible, of which the clinical relevance is unknown.

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. No clinical data on exposed pregnancies are available. 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 is expected to have 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, the following adverse reactions were found to be associated with Ovitrelle in a dose-related fashion: OHSS, vomiting and nausea. 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  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 anaphylactic reactions and shock

##### Psychiatric disorders

Uncommon: Depression, irritability, restlessness

##### Nervous system disorders

Common: Headache

##### Vascular disorders

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

##### Gastrointestinal disorders

Common: Vomiting, nausea, abdominal pain

Uncommon: Diarrhoea

##### Skin and subcutaneous tissue disorders

Very rare: Mild reversible skin reactions manifesting as rash

##### Reproductive system and breast disorders

Common: Mild or moderate OHSS

Uncommon: Severe OHSS, breast pain

##### General disorders and administration site conditions

Common: Tiredness, injection site reactions.

Ectopic pregnancy, ovarian torsion and other complications have been reported in patients after hCG administration. These are considered concomitant effects related to assisted reproductive techniques.

#### 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 listed in [Appendix V](#).

#### **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 techniques, 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

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/00/165/007

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 02 February 2001  
Date of latest renewal: 02 February 2006

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.