Ovitrelle® 250 mcg

1. NAME OF THE MEDICINAL PRODUCT

Ovitrelle® 250 micrograms/0.5 ml, solution for injection in a pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Choriogonadotropin alfa*  250 micrograms in 0.5 ml. (equivalent to approximately 6500 IU)

* Produced by recombinant DNA technology in CHO

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear colourless solution.

The pH of the solution is 7.0 ± 0.3, its osmolarity 250-400 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovitrelle® is indicated in the treatment of

(i) 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,

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

4.2 Posology and method of administration

Ovitrelle is intended for subcutaneous administration.

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

The following dosing 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 an FSH- or 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.
4.3 Contraindications

Ovitrelle is contraindicated for safety reasons in case of:
- Tumours of the hypothalamus and pituitary gland
- Hypersensitivity to the active substance or to any of the excipients
- 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 thrombo-embolic disorders

Ovitrelle must not be used when an effective response cannot be obtained, for example:
- 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

To date, there is no clinical experience with Ovitrelle in other indications commonly treated with urine derived human chorionic gonadotropin.

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.

Special precautions should be taken before administering Ovitrelle to patients with clinically significant systemic disease where pregnancy could lead to a worsening of the condition.

Patients undergoing ovarian stimulation are at an increased risk of developing ovarian hyperstimulation syndrome (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 and the presence of ascites within a clinical picture of circulatory dysfunction. Ovarian hyperstimulation syndrome due to excessive ovarian response can be avoided by withholding hCG administration. Patients should be advised to refrain from coitus or use barrier methods for at least 4 days.

Careful monitoring of estradiol levels and ovarian response, based on ultrasound is recommended prior to and during stimulation therapy, for all patients.

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

To minimise the risk of OHSS and of multiple pregnancy, ultrasound scans as well as estradiol measurements are recommended. 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 > 3000 pg/ml (11000 pmol/l) and 20 or more follicles of 12 mm or more in diameter. When the estradiol level is > 5500 pg/ml (20000 pmol/l) and when there are 40 or more follicles in total, it may be necessary to withhold hCG administration.

Severe ovarian hyperstimulation syndrome could be complicated in rare cases by haemoperitoneum, acute pulmonary distress, ovarian torsion, and thromboembolism.

Adherence to recommended Ovitrelle dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation and multiple pregnancy.

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.

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

Self-administration of Ovitrelle should only be performed by patients who are adequately trained and have access to expert advice.
4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies with Ovitrelle and other medicines have been performed however no clinically significant drug interactions have been reported during hCG therapy. Following administration, Ovitrelle may interfere for up to ten days with the immunological determination of serum / urinary hCG, leading to a false positive pregnancy test.

4.6 Pregnancy and lactation

Considering the indication, Ovitrelle should not be administrated during pregnancy and lactation. For Ovitrelle 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. There are no data on the excretion of choriogonadotropin alfa in milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In comparative trials with different doses of Ovitrelle, the following undesirable effects were found to be associated with Ovitrelle in a dose-related fashion: ovarian hyperstimulation syndrome, and vomiting and nausea. Ovarian hyperstimulation syndrome was observed in approximately 4% of patients treated with Ovitrelle. Severe ovarian hyperstimulation syndrome was reported in less than 0.5% patients (section 4.4).

In rare instances, thromboembolisms have been associated with menotropin/hCG therapy. Although this adverse event was not observed, there is the possibility that this may also occur with Ovitrelle.

Ectopic pregnancy, ovarian torsion and other complications have been reported in patients after hCG administration. These are considered concomitant effects related to Assisted Reproductive Technologies (ART).

After best evidence assessment, the following undesirable effects may be observed after administration of Ovitrelle. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Common (>1/100, <1/10)

**Gastro-intestinal disorders:** Vomiting/nausea, abdominal pain
**Reproductive system and breast disorders:** Mild or moderate ovarian hyperstimulation syndrome.
**General disorders and administration site conditions:** Headache, tiredness, Local reaction/pain at injection site.

Uncommon (>1/1000, <1/100)

**Psychiatric disorders:** Depression, irritability, restlessness,
**Gastro-intestinal disorders:** Diarrhoea,
**Reproductive disorders and breast disorders:** Severe ovarian hyperstimulation syndrome, breast pain.

Very rare (<1/10,000)

**Immune system disorders:** allergic reactions
**Skin and subcutaneous tissue disorders:** Mild reversible skin reactions manifesting as rash.

4.9 Overdose

No case of overdose has been reported.

Nevertheless, there is a possibility that ovarian hyperstimulation syndrome (OHSS) may result from an overdosage of Ovitrelle (see section 4.4).
5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmaco-therapeutic group: gonadotropins, ATC code: G03GA08

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 to the ovarian theca (and granulosa) cells to a transmembrane receptor shared with the luteinising hormone, the LH/CG receptor.

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 LH-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.

In comparative clinical trials, administration of a dose of 250 micrograms of Ovitrelle was as effective as 5000 IU and 10000 IU of urinary hCG in inducing final follicular maturation and early luteinisation in assisted reproductive techniques, and as effective as 5000 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 currently registered freeze-dried formulation and the liquid formulation showed bioequivalence between the two formulations.

5.3 **Preclinical safety data**

Non-clinical 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 drug 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
L-methionine
Poloxamer
Diluted phosphoric acid
Sodium hydroxide
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**

After opening, the 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 at 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

Only clear solution without particles should be used. Any unused product or waste material should be disposed of in accordance with local requirements.

For single use only.

Manufacturer: Merck Serono S.A. Geneva, Switzerland
Registration Holder: Merck Serono Ltd., 50 Basel St., Herzliya

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