PROFESSIONAL INFORMATION

OVITRELLE 250 µg/0,5 ml (injection)

SCHEDULING STATUS

Schedule 4

PROPRIETARY NAME (AND DOSAGE FORM)

OVITRELLE 250 µg/0,5 ml (injection)

COMPOSITION

Each pre-filled pen of **OVITRELLE 250 µg/0,5 ml** injection contains 250 micrograms of choriogonadotropin alfa per 0,5 ml. A dose of 250 micrograms is equivalent to approximately 6500 IU. Inactive components: mannitol, L-methionine, poloxamer 188, phosphoric acid, sodium hydroxide and water for injections.

PHARMACOLOGICAL CLASSIFICATION

A 21.10 Trophic hormones

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Pharmacotherapeutic Group: ATC code: G03GA08

OVITRELLE 250 µg/0,5 ml is a medicinal product of chorionic gonadotropin produced by recombinant DNA techniques.

It shares the amino acid sequence with urinary human Chorionic Gonadotropin (hCG). Chorionic gonadotropin binds on the ovarian theca (and granulosa) cells to a transmembrane receptor

shared with the luteinising hormone, the Luteinising hormone (LH)/Chorionic Gonadotropin (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 250 µg/0,5 ml 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 250 µg/0,5 ml** 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 250 µg/0,5 ml**.

Repeated exposure to **OVITRELLE 250 µg/0,5 ml** was investigated in male patients only.

Clinical investigation in women for the indication of assisted reproductive technologies (ART) and anovulation was limited to one treatment cycle.

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 %.

INDICATIONS

OVITRELLE 250 µg/0,5 ml is indicated in the treatment of:

i) Women undergoing superovulation prior to assisted reproductive techniques such as in vitro fertilisation (IVF): **OVITRELLE 250 µg/0,5 ml** is administered to trigger final follicular maturation and luteinisation after stimulation of follicular growth.

ii) Anovulatory or oligo-ovulatory women: **OVITRELLE 250 µg/0,5 ml** is administered to trigger ovulation and luteinisation in anovulatory or oligo-ovulatory patients after stimulation of follicular growth.

CONTRA-INDICATIONS

OVITRELLE 250 µg/0,5 ml is contra-indicated 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.
- Extra-uterine pregnancy in the previous 3 months.
- Recent or history of thrombo-embolic disorders.

OVITRELLE 250 µg/0,5 ml 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.

WARNINGS AND SPECIAL PRECAUTIONS

To date, there is no clinical experience with **OVITRELLE 250 µg/0,5 ml** in other indications commonly treated with urine derived human chorionic gonadotrophin.

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contra-indications 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 250 µg/0,5 ml** to patients with clinically significant systemic disease where pregnancy could lead to a worsening of the condition, for example, any woman treated for a chronic disease and for whom the wish to become pregnant would mean the discontinuation of medication and therefore a worsening of her underlying medical condition (e.g. epilepsy, diabetes or cardiac disorders).

Self-administration of **OVITRELLE 250 µg/0,5 ml** should only be performed by patients who are adequately trained and have access to expert advice.

Ovarian Hyperstimulation Syndrome (OHSS)

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, or the presence of ascites within a clinical picture of circulatory dysfunction.

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 > 3000pg/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.

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.
To minimise the risk of OHSS and of multiple pregnancy, ultrasound scans as well as estradiol measurements are recommended.

Thromboembolic events

In women with recent or ongoing thromboembolic disease or women with generally recognized risk factors for thromboembolic events, such as personal or family history, treatment with gonadotrophins may further increase the risk of aggravation or occurrence of such events. In these women, the benefits of gonadotrophin 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.

Multiple pregnancy

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. Adherence to recommended **OVITRELLE 250 µg/0,5 ml** dosage, regimen of administration and careful monitoring of therapy will minimise the incidence of ovarian hyperstimulation 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.

Effects on ability to drive and use machines

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

INTERACTIONS

No clinically significant interactions have been reported during hCG therapy.

Following administration, **OVITRELLE 250 µg/0,5 ml** may interfere for up to ten days with the immunological determination of serum / urinary hCG, leading to a false positive pregnancy test. During **OVITRELLE 250 µg/0,5 ml** injection therapy, minor thyroid stimulation is possible of which the clinical relevance is unknown.

PREGNANCY AND LACTATION

Pregnancy

Considering the indication, **OVITRELLE 250 µg/0,5 ml** should not be used during pregnancy and lactation. For **OVITRELLE 250 µg/0,5 ml** no clinical data on exposed pregnancies are available. No reproduction studies with choriogonadotropin alfa in animals were performed. The potential risk for humans is unknown.

Lactation

There are no data on the excretion of choriogonadotropin alfa in milk.

DOSAGE AND DIRECTIONS FOR USE

OVITRELLE 250 µg/0,5 ml is intended for subcutaneous administration.

Treatment with **OVITRELLE 250 µg/0,5 ml** should be performed under the supervision of a medical practitioner experienced in the treatment of fertility problems.

The following dosing regimen should be applied:

i) *Women undergoing superovulation prior to assisted reproductive techniques, such as in vitro fertilisation* (*IVF):*

One pre-filled pen of **OVITRELLE 250 µg/0,5 ml** 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.

ii) Anovulatory or oligo-ovulatory women:

One pre-filled pen of **OVITRELLE 250 µg/0,5 ml** 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 injection of **OVITRELLE 250 µg/0,5 ml**.

OVITRELLE 250 µg/0,5 ml is for single use only.
Any unused product or waste material should be disposed of in accordance with local requirements.

SIDE-EFFECTS

OVITRELLE 250 µg/0,5 ml is used to trigger final follicular maturation and early luteinisation after use of medicinal products for the stimulation of follicular growth. In this context it is difficult to attribute undesirable effects to any one of the products used.

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).

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 250 µg/0,5 ml**.

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

ii) Uncommon (≥*1/1000, < 1/100)*

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

iii) Very rare (≤1/10000)

Immune system disorders:	Allergic reactions
Skin and subcutaneous tissue disorders:	Mild reversible skin reactions manifesting as rash.
Vascular disorders:	Thromboembolism (both in association with and separate from OHSS)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No case of overdosage has been reported.

Nevertheless, there is a possibility that ovarian hyperstimulation syndrome (OHSS) may result from an overdosage of **OVITRELLE 250 µg/0,5 ml** (See: **SIDE-EFFECTS AND WARNINGS AND SPECIAL PRECAUTIONS**).

IDENTIFICATION

OVITRELLE 250 µg/0,5 ml injection in a pre-filled pen - A clear colourless solution in a cartridge composed of a neutral, colourless Type 1 borosilicate glass barrel (nominal capacity of 3 ml) with an aluminium crimp and a bromobutyl rubber plunger stopper. The pen injector is a disposable administration device and is pre-assembled with the cartridge.

PRESENTATION

OVITRELLE 250 µg/0,5 ml is supplied in a pack of a single pre-filled pen and an injection needle.

STORAGE INSTRUCTIONS

Keep out of reach of children.

Store in a refrigerator at 2° - 8 °C.

Store in the original package.

OVITRELLE 250 µg/0,5 ml injection can be stored by the patient below 25°C for up to 30 days.

REGISTRATION NUMBER

OVITRELLE 250 µg/0,5 ml

41/21.10/0523.

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE

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