## 1. NAME OF THE MEDICINAL PRODUCT

**ELONVA® 100 mcg /0.5 ml**
**ELONVA® 150 mcg /0.5 ml**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 100 or 150 micrograms of corifollitropin alfa* in 0.5 mL solution for injection.

*corifollitropin alfa is a glycoprotein produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Excipient(s) with known effect:
This medicinal product contains less than 1 mmol sodium (23 mg) per injection, that is to say, essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear and colourless aqueous solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Elonva is indicated for Controlled Ovarian Stimulation (COS) in combination with a Gonadotropin Releasing Hormone (GnRH) antagonist for the development of multiple follicles in women participating in an Assisted Reproductive Technology (ART) program.

### 4.2 Posology and method of administration

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

*Posology*

In the treatment of women of reproductive age, the dose of Elonva is based on weight and age.

- A single 100-microgram dose is recommended in women who weigh less than or equal to 60 kilograms and who are 36 years of age or younger.

- A single 150-microgram dose is recommended in women:
  - who weigh more than 60 kilograms, regardless of age.
  - who weigh 50 kilograms or more and who are older than 36 years of age.

Women older than 36 years of age who weighed less than 50 kilograms were not studied.

| | | Body Weight | | |
|---|---|---|---|---|
| | | Less than 50 kg | 50 – 60 kg | More than 60 kg |
| Age | 36 years or younger | 100 micrograms | 100 micrograms | 150 micrograms |
| | Older than 36 years | Not studied. | 150 micrograms | 150 micrograms |

The recommended doses of Elonva have only been established in a treatment cycle with a GnRH antagonist that was administered from stimulation day 5 or day 6 onwards (see also sections 4.1, 4.4, and 5.1).

Stimulation day 1:
Elonva should be administered as a single subcutaneous injection, preferably in the abdominal wall, during the early follicular phase of the menstrual cycle.

Stimulation day 5 or 6:
Treatment with a GnRH antagonist should be started on stimulation day 5 or day 6 depending on the ovarian response, i.e. the number and size of growing follicles. The concurrent determination of serum oestradiol levels may also be useful. The GnRH antagonist is used to prevent premature Luteinising Hormone (LH) surges.

Stimulation day 8:
Seven days after the injection with Elonva on stimulation day 1, COS treatment may be continued with daily injections of (recombinant) Follicle Stimulating Hormone [(rec)FSH] until the criterion for triggering final oocyte maturation (3 follicles ≥ 17 mm) has been reached. The daily dose of (rec)FSH may depend on the ovarian response which should be monitored by regular ultrasongraphic assesments from stimulation day 5 or 6 onwards. In normal responders a daily dose of 150 IU (rec)FSH is advised. Administration of (rec)FSH on the day of human Chorionic Gonadotropin (hCG) administration can be omitted, depending on the ovarian response. In general, adequate follicular development is achieved on average by the ninth day of treatment (range 6 to 18 days).

As soon as three follicles ≥ 17 mm are observed, a single injection of 5,000 up to 10,000 IU hCG is administered the same day or the day thereafter to induce final oocyte maturation. In case of an excessive ovarian response, see the recommendations given in section 4.4 in order to reduce the risk for developing ovarian hyperstimulation syndrome (OHSS).

*Special populations*

Renal impairment
No clinical studies have been performed in patients with renal insufficiency. Since the rate of elimination of corifollitropin alfa may be reduced in patients with renal insufficiency, the use of Elonva in these women is not recommended (see sections 4.4 and 5.2).

Hepatic impairment
Although data in hepatically impaired patients are not available, hepatic impairment is unlikely to affect the elimination of corifollitropin alfa (see section 5.2).

*Paediatric population*

There is no relevant use of Elonva within the approved indication in the paediatric population.

Method of administration

Subcutaneous injection of Elonva may be carried out by the woman herself or her partner, provided that proper instructions are given by the physician. Self administration of Elonva should only be performed by women who are well-motivated, adequately trained and with access to expert advice.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Tumours of the ovary, breast, uterus, pituitary or hypothalamus.
- Abnormal (not menstrual) vaginal bleeding without a known/diagnosed cause.
- Primary ovarian failure.
- Ovarian cysts or enlarged ovaries.
- Fibroid tumours of the uterus incompatible with pregnancy.
- Malformations of the reproductive organs incompatible with pregnancy.
- Risk factors for OHSS:
- A history of Ovarian Hyperstimulation Syndrome (OHSS).
- A previous COS cycle that resulted in more than 30 follicles $\geq$ 11 mm measured by ultrasound examination.
    - A basal antral follicle count > 20.
    - Polycystic ovarian syndrome (PCOS).

## 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.

Infertility evaluation before starting treatment

Before starting treatment, the couple's infertility should be assessed as appropriate. In particular, women should be evaluated for hypothyroidism, adrenocortical insufficiency, hyperprolactinemia and pituitary or hypothalamic tumours, and appropriate specific treatment given. Medical conditions that contraindicate pregnancy should also be evaluated before starting treatment with Elonva.

Dosing during the stimulation cycle

Elonva is intended for single subcutaneous injection only. Additional injections of Elonva should not be given within the same treatment cycle. (See also section 4.2.)

After administration of Elonva, no additional FSH-containing product should be administered prior to stimulation day 8 (see also section 4.2).

Renal insufficiency

In patients with mild, moderate or severe renal insufficiency the rate of elimination of corifollitropin alfa may be reduced (see sections 4.2 and 5.2). Therefore, the use of Elonva in these women is not recommended.

Not recommended with a GnRH agonist protocol

There are limited data on the use of Elonva in combination with a GnRH agonist. Results of a small uncontrolled study suggest a higher ovarian response than in combination with a GnRH antagonist. Therefore, the use of Elonva is not recommended in combination with a GnRH agonist (see also section 4.2).

Ovarian hyperstimulation syndrome (OHSS)
OHSS is a medical event distinct from uncomplicated ovarian enlargement. Clinical signs and symptoms of mild and moderate OHSS are abdominal pain, nausea, diarrhoea, mild to moderate enlargement of ovaries and ovarian cysts. Severe OHSS may be life-threatening. Clinical signs and symptoms of severe OHSS are large ovarian cysts, acute abdominal pain, ascites, pleural effusion, hydrothorax, dyspnoea, oliguria, haematological abnormalities and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS. Transient liver function test abnormalities suggestive of hepatic dysfunction with or without morphologic changes on liver biopsy have also been reported in association with OHSS. OHSS may be caused by administration of hCG and by pregnancy (endogenous hCG). Early OHSS usually occurs within 10 days after hCG administration and may be associated with an excessive ovarian response to gonadotropin stimulation. Late OHSS occurs more than 10 days after hCG administration, as a consequence of the hormonal changes with pregnancy. Because of the risk of developing OHSS, patients should be monitored for at least two weeks after hCG administration.

Women with known risk factors for a high ovarian response may be especially prone to the development of OHSS following treatment with Elonva. For women having their first cycle of ovarian stimulation, for whom risk factors are only partially known, close observation for early signs and symptoms of OHSS is recommended.
Follow current clinical practice for reducing the risk of OHSS during Assisted Reproductive Technology (ART). Adherence to the recommended Elonva dose and treatment regimen and careful monitoring of ovarian response is important to reduce the risk of OHSS.

To monitor the risk of OHSS, ultrasonographic assessments of follicular development should be performed prior to treatment and at regular intervals during treatment; the concurrent determination of serum oestradiol levels may also be useful. In ART there is an increased risk of OHSS with 18 or more follicles of 11 mm or more in diameter.

If OHSS develops, standard and appropriate management of OHSS should be implemented and followed.

Ovarian torsion
Ovarian torsion has been reported after treatment with gonadotropins, including Elonva. Ovarian torsion may be related to other conditions, such as OHSS, pregnancy, previous abdominal surgery, past history of ovarian torsion, and previous or current ovarian cysts. Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion.

Multiple pregnancy

Multiple pregnancies and births have been reported for all gonadotropin treatments, including Elonva. The woman and her partner should be advised of the potential risks for the mother (pregnancy and delivery complications) and the neonate (low birth weight) before starting treatment. In women undergoing ART procedures the risk of multiple pregnancy is mainly related to the number of embryos transferred.

Ectopic pregnancy

Infertile women undergoing ART have an increased incidence of ectopic pregnancies. 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.

Ovarian and other 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 treatment. It is not established whether or not treatment with gonadotropins increases the risk of these tumours in infertile women.

Vascular complications
Thromboembolic events, both in association with and separate from OHSS, have been reported following treatment with gonadotropins, including Elonva. Intravascular thrombosis, which may originate in venous or arterial vessels, can result in reduced blood flow to vital organs or the extremities.In women with generally recognized risk factors for thromboembolic events, such as a personal or family history, severe obesity or thrombophilia, treatment with gonadotropins may further increase this risk. In these women the benefits of gonadotropin administration need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per injection, that is to say essentially ‘sodium-free’.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with Elonva and other medicines have been performed. Since corifollitropin alfa is not a substrate of cytochrome P450 enzymes, no metabolic interactions with other medicinal products are anticipated.

Elonva may cause a false positive hCG pregnancy test if the test is administered during the ovarian stimulation portion of the ART cycle. This may be due to cross-reactivity of some hCG pregnancy tests with the carboxy-terminal peptide of the beta subunit of Elonva.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
In case of inadvertent exposure to Elonva during pregnancy, clinical data are not sufficient to exclude an adverse outcome of pregnancy. In animal studies reproductive toxicity has been observed (see preclinical safety data in section 5.3). The use of Elonva during pregnancy is not indicated.

Breast-feeding
The use of Elonva during breast-feeding is not indicated.

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

## 4.7 Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been performed.
Elonva may cause dizziness. Women should be advised that if they feel dizzy, they should not drive or use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions during treatment with Elonva in clinical trials (N=2,397) are pelvic discomfort (6.0%), OHSS (4.3%, see also section 4.4), headache (4.0%), pelvic pain (2.9%), nausea (2.3%), fatigue (1.5%) and breast tenderness (1.3%).

Tabulated list of adverse reactions

The table below displays the main adverse reactions in women treated with Elonva in clinical trials and post-marketing surveillance according to system organ class and frequency; 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) and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| System organ class | Frequency | Adverse reaction |
|---|---|---|
| **Immune system disorders** | Not known | Hypersensitivity reactions, both local and generalised, including rash* |
| **Psychiatric disorders** | Uncommon | Mood swings |
| **Nervous system disorders** | Common | Headache |
| | Uncommon | Dizziness |
| **Vascular disorders** | Uncommon | Hot flush |
| **Gastrointestinal disorders** | Common | Nausea |
| | Uncommon | Abdominal distension, vomiting, diarrhoea, constipation |
| **Musculoskeletal and connective tissue disorders** | Uncommon | Back pain |
| **Pregnancy, puerperium and perinatal conditions** | Uncommon | Abortion spontaneous |
| **Reproductive system and breast disorders** | Common | OHSS, pelvic pain, pelvic discomfort, breast tenderness |
| | Uncommon | Ovarian torsion, adnexa uteri pain, premature ovulation, breast pain |
| **General disorders and administration site conditions** | Common | Fatigue |
| | Uncommon | Injection site haematoma, injection site pain, irritability |
| **Investigations** | Uncommon | Alanine aminotransferase increased, aspartate |

| | | |
|---|---|---|
| | | aminotransferase increased |
| **Injury, poisoning and procedural complications** | Uncommon | Procedural pain |

*Adverse reactions were identified through post-marketing surveillance.

Description of selected adverse reactions

In addition, ectopic pregnancy and multiple gestations have been reported. These are considered to be related to ART or subsequent pregnancy.

In rare instances, thromboembolism has been associated with Elonva therapy as with other gonadotropins.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

## 4.9 Overdose

More than one injection of Elonva within one treatment cycle or too high a dose of Elonva and/or (rec)FSH may increase the risk of OHSS. (see OHSS in section 4.4.)

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system, gonadotropins
ATC code: G03GA09

Mechanism of action

Corifollitropin alfa is designed as a sustained follicle stimulant with the same pharmacodynamics profile as (rec)FSH, but with a markedly prolonged duration of FSH activity. Due to its ability to initiate and sustain multiple follicular growth for an entire week, a single subcutaneous injection of the recommended dose of Elonva may replace the first seven injections of any daily (rec)FSH preparation in a COS treatment cycle. The long duration of FSH activity was achieved by adding the carboxy-terminal peptide of the β-subunit of human chorionic gonadotropin (hCG) to the β-chain of human FSH. Corifollitropin alfa does not display any intrinsic LH/hCG activity.

Clinical efficacy and safety

In three randomized, double-blind, clinical trials, treatment with a single subcutaneous injection of Elonva, 100 micrograms (ENSURE study) or 150 micrograms (ENGAGE and PURSUE study), for the first seven days of COS was compared to treatment with a daily dose of 150, 200, or 300 IU of recFSH, respectively. Pituitary suppression with a GnRH antagonist (ganirelix acetate injection at a daily dose of 0.25 mg) was used in each of the three clinical trials.

In the ENSURE study, 396 healthy normal ovulatory women, aged 18 to 36 years with a body weight less than or equal to 60 kg, were treated for one cycle with 100 micrograms of Elonva and pituitary suppression with a GnRH antagonist as part of an ART program. The primary efficacy endpoint was number of oocytes retrieved. The median total duration of stimulation was 9 days for both groups, indicating that two days of recFSH were required to complete ovarian stimulation from stimulation day 8 onwards (recFSH was given on the day of hCG for this study).

In the ENGAGE Study, 1,506 healthy normal ovulatory women, aged 18 to 36 years with a body weight greater than 60 kg and less than or equal to 90 kg, were treated for one cycle with 150 micrograms of Elonva and pituitary suppression with a GnRH antagonist as part of an ART program. The co-primary efficacy endpoints were ongoing pregnancy rate and number of oocytes retrieved. The median total duration of stimulation was 9 days for both groups, indicating that two days of recFSH were required to complete ovarian stimulation from stimulation day 8 onwards (recFSH was given on the day of hCG for this study).

In the PURSUE study, 1,390 healthy normal ovulatory women, aged 35 to 42 years with a body weight greater than or equal to 50 kg, were treated for one cycle with 150 micrograms of Elonva and pituitary suppression with a GnRH antagonist as part of an ART program. The primary efficacy endpoint was vital pregnancy rate. The number of oocytes retrieved was a key secondary efficacy endpoint. The median total duration of stimulation was 9 days for both groups, indicating that one day of recFSH was required to complete ovarian stimulation from stimulation day 8 onwards (no recFSH was given on the day of hCG for this study).

*Number of oocytes retrieved*
In all three studies, treatment with a single injection of Elonva, 100 or 150 micrograms, for the first seven days of COS, resulted in a higher number of oocytes retrieved compared with a daily dose of recFSH. However, the differences were within the predefined equivalence (ENGAGE and ENSURE) or non-inferiority (PURSUE) margins. See Table 1 below.

**Table 1: Mean Number of Oocytes Retrieved from ENSURE, ENGAGE, and PURSUE Intent-to-Treat Population (ITT)**

| **Parameter** | **ENSURE** (18-36 years of age) (body weight less than or equal to 60 kg) | | **ENGAGE** (18-36 years of age) (body weight greater than 60 kg and less than or equal to 90 kg) | | **PURSUE** (35-42 years of age) (body weight greater than or equal to 50 kg) | |
|---|---|---|---|---|---|---|
| | **Elonva 100 µg** | **recFSH 150 IU** | **Elonva 150 µg** | **recFSH 200 IU** | **Elonva 150 µg** | **recFSH 300 IU** |
| | N=268 | N=128 | N=756 | N=750 | N=694 | N=696 |
| Mean number of oocytes | 13.3 | 10.6 | 13.8 | 12.6 | 10.7 | 10.3 |
| Difference [95% CI] | 2.5 [1.2; 3.9] | | 1.2 [0.5, 1.9] | | 0.5 [-0.2, 1.2] | |

*Pregnancy from the fresh cycles of ENGAGE and PURSUE*
In the ENGAGE study, non-inferiority was demonstrated in ongoing pregnancy rates between Elonva and recFSH, with ongoing pregnancy rate defined as presence of at least one foetus with heart activity assessed at least 10 weeks after embryo transfer.

In the PURSUE study, non-inferiority was demonstrated in vital pregnancy rate between Elonva and recFSH, with vital pregnancy rate defined as the percentage of subjects with at least one foetus with heart activity assessed 5 to 6 weeks after embryo transfer.

The pregnancy results from the fresh cycles of ENGAGE and PURSUE are summarized in Table 2 below.

**Table 2: Pregnancy Results from the Fresh Cycles of ENGAGE and PURSUE Intent-to-Treat Population (ITT)**

| **Parameter** | **Fresh Cycles of ENGAGE**[†] (18-36 years of age) (body weight greater than 60 kg and less than or equal to 90 kg) | | | **Fresh Cycles of PURSUE**[‡] (35-42 years of age) (body weight greater than or equal to 50 kg) | | |
|---|---|---|---|---|---|---|
| | **Elonva 150 µg** | **recFSH 200 IU** | **Difference [95% CI]** | **Elonva 150 µg** | **recFSH 300 IU** | **Difference [95% CI]** |
| | N=756 | N=750 | | N=694 | N=696 | |
| Vital pregnancy rate | 39.9% | 39.1% | 1.1 [-3.8, 5.9] | 23.9% | 26.9% | -3.0 [-7.3, 1.4] |
| Ongoing pregnancy rate | 39.0% | 38.1% | 1.1 [-3.8, 5.9] | 22.2% | 24.0% | -1.9 [-6.1, 2.3] |
| Live birth rate* | 35.6% | 34.4% | 1.3 [-3.5, 6.1] | 21.3% | 23.4% | -2.3 [-6.5, 1.9] |

[†]The primary efficacy endpoint in the ENGAGE study was ongoing pregnancy (assessed at least 10 weeks after embryo transfer).
[‡]The primary efficacy endpoint in the PURSUE study was vital pregnancy rate defined as the percentage of subjects with at least one foetus with heart activity assessed 5 to 6 weeks after embryo transfer.
*Live birth rate was a secondary efficacy endpoint in ENGAGE and PURSUE.

In these clinical trials, the safety profile of a single injection with Elonva was comparable to daily injections with recFSH.

*Pregnancy from the Frozen-Thawed Embryo Transfer (FTET) cycles of ENGAGE and PURSUE*

The follow-up FTET trial for ENGAGE included women who had at least one embryo thawed for use up to at least one year after cryopreservation. The mean number of embryos transferred in the FTET cycles of ENGAGE was 1.7 in both treatment groups.

The follow-up FTET trial for PURSUE included women who had at least one embryo thawed for use within two years of the date of the last cryopreservation for this trial. The mean number of embryos transferred in the FTET cycles of PURSUE was 2.4 in both treatment groups. This trial also provided safety data on the infants born from cryopreserved embryos.

The maximum number of FTET cycles was 5 and 4 for the follow-up FTET trial for ENGAGE and PURSUE, respectively. The pregnancy results from the first two FTET cycles of ENGAGE and PURSUE are summarized in Table 3 below.

**Table 3: Pregnancy Results from the FTET cycles of ENGAGE and PURSUE Intent-to-Treat Population (ITT)**

| | **FTET Cycles of ENGAGE (18-36 years of age) (body weight greater than 60 kg and less than or equal to 90 kg)** | | **FTET Cycles of PURSUE (35-42 years of age) (body weight greater than or equal to 50 kg)** | |
|---|---|---|---|---|
| | **Elonva** | **recFSH** | **Elonva** | **recFSH** |

| | 150 µg | | | 200 IU | | | 150 µg | | | 300 IU | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **n** | **N** | **%** | **n** | **N** | **%** | **n** | **N** | **%** | **n** | **N** | **%** |
| **FTET Cycle 1a** | | | | | | | | | | | | |
| Ongoing pregnancy | 55 | 148 | 37.2 | 45 | 147 | 30.6 | 43 | 152 | 28.3 | 42 | 145 | 29.0 |
| Live birth | - | - | - | - | - | - | 43 | 152 | 28.3 | 41 | 145 | 28.3 |
| **FTET Cycle 2a** | | | | | | | | | | | | |
| Ongoing pregnancy | 9 | 38 | 23.7 | 9 | 31 | 29.0 | 8 | 23 | 34.8 | 6 | 14 | 42.9 |
| Live birth | - | - | - | - | - | - | 8 | 23 | 34.8 | 6 | 14 | 42.9 |

n = number of subjects with the event; N = total number of subjects
a Per embryo transfer.

*Congenital malformations reported in infants born after a frozen-thawed embryo transfer (FTET) cycle*
Following use of Elonva, 61 infants were born after an FTET cycle in the PURSUE study follow-up, and 607 infants were born after fresh ART cycles in the ENSURE, ENGAGE and PURSUE studies combined. The rates for congenital malformations (major and minor combined) reported for infants born after an FTET cycle in the PURSUE study follow-up (16.4%) were similar to those reported for infants born after fresh ART cycles in the ENSURE, ENGAGE and PURSUE studies combined (16.8%).

*Immunogenicity*
Of the 2,511 women treated with Elonva who were evaluated for the formation of post-treatment antibodies, four (0.16%) had evidence of antibody formation, including three who had been exposed once to Elonva and one who had been exposed twice to Elonva. In each case, these antibodies were non-neutralizing and did not interfere with the response to stimulation or the normal physiologic responses of the Hypothalamic-Pituitary-Ovarian (HPO) axis. Two of these four women became pregnant during the same treatment cycle in which antibodies were detected, suggesting that the presence of non-neutralizing antibodies after stimulation with Elonva is not clinically relevant.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Elonva in one or more subsets of the paediatric population in hypogonadotrophic hypogonadism. (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Pharmacokinetic parameters of corifollitropin alfa were evaluated after subcutaneous administration in women undergoing a COS treatment cycle.

Due to the long elimination half-life, after administration of the recommended dose, serum concentrations of corifollitropin alfa are sufficient to sustain multiple follicular growth for an entire week. This justifies replacement of the first seven injections of daily (rec)FSH with a single subcutaneous injection of Elonva in COS for the development of multiple follicles and pregnancy in an ART program (see section 4.2).

Body weight is a determinant of exposure to corifollitropin alfa. Corifollitropin alfa exposure after a single subcutaneous injection is 665 hours*ng/mL (AUC, 426-1,037 hours*ng/mL[1]) and is similar after administration of 100 micrograms corifollitropin alfa to women with a body weight less than or equal to 60 kilograms and of 150 micrograms corifollitropin alfa to women with a body weight greater than 60 kilograms.

Absorption

After a single subcutaneous injection of Elonva, the maximum serum concentration of corifollitropin alfa is 4.24 ng/mL (2.49-7.21 ng/mL[1]) and is reached 44 hours (35-57 hours[1]) postdose. The absolute bioavailability is 58% (48-70%[1]).

Distribution

Distribution, metabolism and elimination of corifollitropin alfa are very similar to other gonadotropins, such as FSH, hCG and LH. After absorption into the blood, corifollitropin alfa is distributed mainly to the ovaries and the kidneys. The steady state volume of distribution is 9.2 L (6.5-13.1 L[1]). Exposure to corifollitropin alfa increases proportionally with dose within the range of 60 micrograms to 240 micrograms.

Elimination

Corifollitropin alfa has an elimination half-life of 70 hours (59-82 hours[1]) and a clearance of 0.13 L/h (0.10-0.18 L/h[1]). Elimination of corifollitropin alfa predominantly occurs via the kidneys, and the rate of elimination may be reduced in patients with renal insufficiency (see sections 4.2 and 4.4). Hepatic metabolism contributes to a minor extent to the elimination of corifollitropin alfa.

Other special populations

*Hepatic impairment*
Although data in hepatically impaired patients are not available, hepatic impairment is unlikely to affect the pharmacokinetic profile of corifollitropin alfa.

### 5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of single and repeated dose toxicity and safety pharmacology.

Reproduction toxicology studies in rats and rabbits indicated that corifollitropin alfa does not adversely affect fertility. Administration of corifollitropin alfa to rats and rabbits, prior to and directly after mating, and during early pregnancy, resulted in embryotoxicity. In rabbits, when administered prior to mating, teratogenicity has been observed. Both embryotoxicity and teratogenicity are considered a consequence of the superovulatory state of the animal not able to support a number of embryos above a physiological ceiling. The relevance of these findings for the clinical use of Elonva is limited.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sucrose
Sodium citrate dihydrate
L-Methionine
Polysorbate 20
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

### 6.2 Incompatibilities

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

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). For convenience, the patient is allowed to store the product at or below 25°C for a period of not more than 1 month.
Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

### 6.5 Nature and contents of container

Elonva is supplied in pre-filled luerlock syringes of 1 mL (type I hydrolytic glass), closed with a bromobutyl elastomer plunger and a tip cap. The syringe is equipped with an automatic safety system to prevent needle stick injuries after use and is packed together with a sterile injection needle. Each pre-filled syringe contains 0.5 mL solution for injection.

Elonva is available in pack sizes of 1 pre-filled syringe.

### 6.6 Special precautions for disposal and other handling

Do not use Elonva if the solution is not clear.

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

**MANUFACTURER**: NV Organon, Oss, The Netherlands.

**LICENSE HOLDER**: Merck Sharp & Dohme (Israel-1996) company Ltd., P.O.Box 7121, Petah-Tikva 49170.
Drug registration no. listed in the official registry of the Ministry of Health:
ELONVA 100 mcg/0.5 ml: 147.30.33282.
ELONVA 150 mcg/0.5 ml: 147.31.33283.

Revised in May 2020.