

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Elonva 100 micrograms solution for injection

Elonva 150 micrograms solution for injection

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

### Elonva 100 micrograms solution for injection

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

### Elonva 150 micrograms solution for injection

Each pre-filled syringe contains 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.

Elonva is indicated for the treatment of adolescent males (14 years and older) with hypogonadotropic hypogonadism, in combination with human Chorionic Gonadotropin (hCG).

### **4.2 Posology and method of administration**

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

Treatment with Elonva for hypogonadotropic hypogonadism should be initiated and supervised by a physician experienced in the treatment of hypogonadotropic hypogonadism.

### 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 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  $\geq$  17 mm) has been reached. The daily dose of (rec)FSH may depend on the ovarian response. 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  $\geq$  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 patients 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*

In the treatment of adolescent males (14 years and older) with hypogonadotropic hypogonadism, the dose of Elonva is based on body weight.

#### For adolescent males weighing less than or equal to 60 kg

100 micrograms of Elonva once every two weeks for 12 weeks, followed by concomitant administration of Elonva (once every 2 weeks) with hCG. For patients initiating therapy with 100 micrograms, consider increasing the dose if their body weight increases to greater than 60 kg during the course of treatment.

#### For adolescent males weighing more than 60 kg

150 micrograms of Elonva once every two weeks for 12 weeks, followed by concomitant administration of Elonva (once every 2 weeks) with hCG.

Combination therapy with hCG twice weekly (500 – 5000 IU) may be necessary for 52 weeks or longer to achieve adult gonadal development.

There are no data to support safety and efficacy when treatment is used for more than 52 weeks and/or after 17 years of age.

### Method of administration

#### *In females*

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.

### *Paediatric population*

#### *In adolescent males (14 years and older)*

Subcutaneous injection in the abdominal wall may be carried out by the patient or a caregiver, provided they have been appropriately trained. Elonva should be administered once every two weeks, in the morning on the same day of the week in combination with hCG twice weekly (500 – 5000 IU).

## **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 patients is not recommended.

### Not recommended with a GnRH agonist protocol in women undergoing ART

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).

### Not recommended in adolescent males previously treated with GnRH, gonadotropins, or testosterone treatment.

There are no data available in patients previously treated with GnRH, gonadotropins (e.g., hCG, FSH) and androgens (e.g., testosterone, etc.) except for diagnostic testing purposes.

### 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 practise 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 recognised 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.

#### *Paediatric population*

Elevated endogenous FSH levels are indicative of primary testicular failure. Such patients are unresponsive to Elonva/hCG therapy.

After completion of pubertal transition with combined Elonva and hCG treatment, long-term treatment with testosterone is required in HH patients to maintain secondary sexual characteristics. However, follow-up treatment protocols for hormonal support have not been evaluated.

#### 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 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 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 in women:

In women Elonva is used in the treatment of Controlled Ovarian Stimulation in combination with GnRH in ART programs (see section 4.1).

Elonva is indicated for treatment of HH in adolescent males:

In adolescent males (14 years and older), Elonva is used in treatment of hypogonadotropic hypogonadism in combination with hCG (see section 4.1). However, whether this treatment has effect on fertility is unknown.

### **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. Patients 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 in women (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 adults treated with Elonva in clinical trials and post-marketing surveillance according to system organ class and frequency; 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 ( $< 1/10,000$ ), and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

### Paediatric population (14 years and older)

The table below lists the adverse reactions with Elonva reported in a clinical trial in adolescent males (17 patients dosed) according to system organ class and frequency: common ( $\geq 1/100$  to  $< 1/10$ ).

SOC	Frequency <sup>1</sup>	Adverse reaction
Gastrointestinal disorders	Common	Vomiting
Vascular disorders	Common	Hot flush
General disorders and administration site conditions	Common	Injection site pain

<sup>1</sup> Adverse reactions that are reported only once are listed as common because a single report raises the frequency above 1%.

### 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**

### *In females*

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).

### *Paediatric population*

The effects of an overdose of Elonva in the adolescent male population are unknown.

## **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 pharmacodynamic profile as (rec)FSH, but with a markedly prolonged duration of FSH activity. The long duration of FSH activity was achieved by adding the carboxy-terminal peptide of the  $\beta$ -subunit of human chorionic gonadotropin (hCG) to the  $\beta$ -chain of human FSH. Corifollitropin alfa does not display any intrinsic LH/hCG activity.

### *In females*

Due to corifollitropin alfa's 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.

*Paediatric adolescent male population (14 years and older)*

Corifollitropin alfa's sustained FSH activity stimulates the immature Sertoli cells in the testis to initiate gonadal development in support of future spermatogenesis. The combination of FSH with hCG is to initiate puberty with stimulation of Leydig cell function and increase testosterone production until testicular volumes attain adult size.

Clinical efficacy and safety

In three randomised, 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 N=268	recFSH 150 IU N=128	Elonva 150 µg N=756	recFSH 200 IU N=750	Elonva 150 µg N=694	recFSH 300 IU 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 summarised 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 <sup>†</sup> (18-36 years of age) (body weight greater than 60 kg and less than or equal to 90 kg)			Fresh Cycles of PURSUE <sup>‡</sup> (35-42 years of age) (body weight greater than or equal to 50 kg)		
	Elonva 150 µg N=756	recFSH 200 IU N=750	Difference [95% CI]	Elonva 150 µg N=694	recFSH 300 IU N=696	Difference [95% CI]
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]

<sup>†</sup>The primary efficacy endpoint in the ENGAGE study was ongoing pregnancy (assessed at least 10 weeks after embryo transfer).

<sup>‡</sup>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 summarised 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 150 µg			recFSH 200 IU			Elonva 150 µg			recFSH 300 IU		
	n	N	%	n	N	%	n	N	%	n	N	%
<b>FTET Cycle 1<sup>a</sup></b>												
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
<b>FTET Cycle 2<sup>a</sup></b>												
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

<sup>a</sup> 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

A single-group, open-label efficacy and safety study was conducted to evaluate the treatment with Elonva in combination with hCG to induce and/or restore puberty and to induce and/or restore spermatogenesis in 17 adolescent males aged 14 years and older for the treatment of hypogonadotropic hypogonadism. A priming period with Elonva instead of hCG in adolescents with HH was included to mimic the gonadotropin pattern of normal puberty, stimulating FSH receptors on Sertoli cells with corifollitropin alfa prior to stimulation of LH receptors on Leydig cells with hCG. The study excluded males who had previously received GnRH, gonadotropins or testosterone treatment. Elonva was administered once every 2 weeks for 64 weeks, alone for the first 12 weeks (priming period), followed by 52 weeks in combination with twice weekly doses of hCG (500 to 5000 IU) (combined treatment period).

The primary endpoint for efficacy was shown by increase in testicular volume, measured as the sum of volumes of left and right testes by ultrasound. During the overall treatment period, the increase noted in testicular volume at Week 64 changed from a geometric mean of 1.4 mL to 12.9 mL, mean fold increase of 9.43 (95% CI: 7.44, 11.97). The primary endpoint for safety showed that corifollitropin alfa was generally well tolerated with no cases of confirmed anti-corifollitropin alfa antibodies, no unexpected values or changes in clinical laboratory data or vitals sign assessments (see also section 4.8).

Additional findings at Week 64 included, increased testosterone levels, growth velocity and progression of puberty (Tanner III, IV and V) indicated appropriate responses to hCG. Decreasing anti-müllerian hormone levels and increases in Inhibin B levels were suggestive of initiation of spermatogenesis.

## **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<sup>1</sup>) 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<sup>1</sup>) and is reached 44 hours (35-57 hours<sup>1</sup>) postdose. The absolute bioavailability is 58% (48-70%<sup>1</sup>).

### 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

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<sup>1</sup> Predicted range for 90% of subjects.

(6.5-13.1 L<sup>1</sup>). 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<sup>1</sup>) and a clearance of 0.13 L/h (0.10-0.18 L/h<sup>1</sup>). 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.

#### *Paediatric population*

In a study of adolescent males 14 to less than 18 years of age with hypogonadotropic hypogonadism (n=17) who were administered 100 micrograms (body weight less than or equal to 60 kg) or 150 micrograms (body weight greater than 60 kg) of Elonva once every two weeks, mean serum trough Elonva concentrations (two weeks postdose) were 591 ng/mL when Elonva was administered alone and 600 ng/mL when Elonva was co-administered with hCG (given twice weekly). Elonva serum concentrations were comparable in participants receiving 100 micrograms and 150 micrograms doses of Elonva.

## **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**

Sodium citrate  
Sucrose  
Polysorbate 20  
Methionine  
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**

3 years

### **6.4 Special precautions for storage**

Store in a refrigerator (2°C-8°C).

Do not freeze.

For convenience, the patient is allowed to store the product at or below 25°C for a period of not more than 1 month.

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.

## **7. MARKETING AUTHORISATION HOLDER**

N.V. Organon  
Kloosterstraat 6  
5349 AB Oss  
The Netherlands

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

EU/1/09/609/001  
EU/1/09/609/002

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

Date of first authorisation: 25 January 2010  
Date of latest renewal: 22 August 2014

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

DD month YYYY

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

## **ANNEX II**

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**



**A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturers of the biological active substance

N.V. Organon  
Kloosterstraat 6  
5349 AB Oss  
The Netherlands

N.V. Organon  
Vollenhovermeer 2  
5347 JV Oss  
The Netherlands

Name and address of the manufacturer responsible for batch release

N.V. Organon  
Kloosterstraat 6  
5349 AB Oss  
The Netherlands

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, Section 4.2).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Elonva 100 micrograms solution for injection  
corifollitropin alfa

**2. STATEMENT OF ACTIVE SUBSTANCE**

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

**3. LIST OF EXCIPIENTS**

Other ingredients: sodium citrate, sucrose, polysorbate 20, methionine, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS****Solution for injection**

1 pre-filled syringe with an automatic safety (needle injury prevention) system and a sterile injection needle. 0.5 mL

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For single use only.  
Read the package leaflet before use.  
Subcutaneous use (SC)

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS****Storage by the pharmacist**

Store in a refrigerator. Do not freeze

Storage by the patient

There are two options:

1. Store in a refrigerator. Do not freeze.
2. Store at or below 25°C for a period of not more than 1 month.

Keep the syringe in the outer carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

N.V. Organon  
Kloosterstraat 6  
5349 AB Oss  
The Netherlands

**12. MARKETING AUTHORISATION NUMBERS**

EU/1/09/609/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

<Justification for not including Braille accepted>

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>PRE-FILLED SYRINGE LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION</b>
---

Elonva 100 micrograms injection  
corifollitropin alfa  
SC

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

0.5 mL

<b>6. OTHER</b>
-----------------

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Elonva 150 micrograms solution for injection  
corifollitropin alfa

**2. STATEMENT OF ACTIVE SUBSTANCE**

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

**3. LIST OF EXCIPIENTS**

Other ingredients: sodium citrate, sucrose, polysorbate 20, methionine, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS****Solution for injection**

1 pre-filled syringe with an automatic safety (needle injury prevention) system and a sterile injection needle. 0.5 mL.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For single use only.  
Read the package leaflet before use.  
Subcutaneous use (SC)

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Storage by the pharmacist  
Store in a refrigerator. Do not freeze.

Storage by the patient

There are two options:

1. Store in a refrigerator. Do not freeze.
2. Store at or below 25°C for a period of not more than 1 month.

Keep the syringe in the outer carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

N.V. Organon  
Kloosterstraat 6  
5349 AB Oss  
The Netherlands

**12. MARKETING AUTHORISATION NUMBERS**

EU/1/09/609/002

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

<Justification for not including Braille accepted>

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN



<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>PRE-FILLED SYRINGE LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION</b>
---

Elonva 150 micrograms injection  
corifollitropin alfa  
SC

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

0.5 mL

<b>6. OTHER</b>
-----------------

## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

### **Elonva 100 micrograms solution for injection Elonva 150 micrograms solution for injection corifollitropin alfa**

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Elonva is and what it is used for
2. What you need to know before you use Elonva
3. How to use Elonva
4. Possible side effects
5. How to store Elonva
6. Contents of the pack and other information

#### **1. What Elonva is and what it is used for**

Elonva contains the active ingredient corifollitropin alfa and belongs to the group of medicines called gonadotropic hormones. Gonadotropic hormones play an important role in human fertility and reproduction. One of these gonadotropic hormones is Follicle Stimulating Hormone (FSH), which is needed in women for the growth and development of follicles (small round sacs in your ovaries that contain the eggs) and in adolescent males (14 years and older) for treatment of delayed puberty due to hypogonadotropic hypogonadism (HH), in combination with a medicine called human Chorionic Gonadotropin (hCG).

##### In women

Elonva is used to help achieve pregnancy in women having infertility treatment, such as *in vitro* fertilisation (IVF). IVF involves collecting the eggs from the ovary, fertilising them in the laboratory, and transferring the embryos into the uterus a few days later. Elonva causes the growth and development of several follicles at the same time by a controlled stimulation of the ovaries.

##### In adolescent males (14 years and older)

Elonva is used to bring about the development and function of the testes and induce the development of male sexual characteristics in adolescent males with delayed puberty due to HH.

#### **2. What you need to know before you use Elonva**

##### **Do not use Elonva if you:**

- are allergic (hypersensitive) to corifollitropin alfa or any of the other ingredients of this medicine (listed in section 6)
- have cancer of the ovary, breast, uterus, or brain (pituitary gland or hypothalamus)
- have recently had unexpected vaginal bleeding, other than menstrual, without a diagnosed cause
- have ovaries that do not work because of a condition called primary ovarian failure
- have ovarian cysts or enlarged ovaries
- have malformations of the sexual organs which make a normal pregnancy impossible
- have fibroid tumours in the uterus which make a normal pregnancy impossible

- have risk factor of OHSS (OHSS is a serious medical problem that can happen when the ovaries are overly stimulated. See below for further explanation.):
  - o have polycystic ovarian syndrome (PCOS)
  - o have had ovarian hyperstimulation syndrome (OHSS)
  - o have previously had a treatment cycle of controlled stimulation of the ovaries that resulted in the growth of more than 30 follicles with a size of 11 mm or larger
  - o have a basal antral follicle count (the number of small follicles present in your ovaries at the beginning of a menstrual cycle) higher than 20

## **Warnings and precautions**

Talk to your doctor before using Elonva.

### Ovarian hyperstimulation syndrome (OHSS)

Treatment with gonadotrophic hormones like Elonva may cause ovarian hyperstimulation syndrome (OHSS). This is a serious medical condition where the ovaries are overly stimulated and the growing follicles become larger than normal. In rare cases, severe OHSS may be life-threatening. Therefore, close supervision by your doctor is very important. To check the effects of treatment, your doctor will do ultrasound scans of your ovaries. Your doctor may also check blood hormone levels. (See also section 4.)

OHSS causes fluid to build up suddenly in your stomach and chest areas and can cause blood clots to form. Call your doctor right away if you have:

- severe abdominal swelling and pain in the stomach area (abdomen)
- feeling sick (nausea)
- vomiting
- sudden weight gain due to fluid build up
- diarrhoea
- decreased urine output
- trouble breathing

You may use Elonva only once during the same treatment cycle, otherwise, the chance of having OHSS may increase.

Before starting to use this medicine, tell your doctor if you have ever had ovarian hyperstimulation syndrome (OHSS).

### Ovarian torsion

Ovarian torsion is the twisting of an ovary. Twisting of the ovary could cause the blood flow to the ovary to be cut off.

Before starting to use this medicine, tell your doctor if you:

- have ever had ovarian hyperstimulation syndrome (OHSS).
- are pregnant or think that you may be pregnant.
- have ever had stomach (abdominal) surgery.
- have ever had a twisting of an ovary.
- have past or current cysts in your ovary or ovaries.

### Blood clot (Thrombosis)

Treatment with gonadotrophic hormones like Elonva may (just as pregnancy) increase the risk of having a blood clot (thrombosis). Thrombosis is the formation of a blood clot in a blood vessel.

Blood clots can cause serious medical conditions, such as:

- blockage in your lungs (pulmonary embolus)
- stroke
- heart attack
- blood vessel problems (thrombophlebitis)

- a lack of blood flow (deep venous thrombosis) that may result in a loss of your arm or leg.

Please discuss this with your doctor, before starting treatment, especially if:

- you know you already have an increased chance of having a thrombosis
- you, or anyone in your immediate family, have ever had a thrombosis
- you are severely overweight.

#### Multiple births or birth defects

There is an increased chance of having twins or even more than two babies, even when only one embryo is transferred into the uterus. Multiple pregnancies carry an increased health risk for both the mother and her babies. Multiple pregnancies and specific characteristics of couples with fertility problems (e.g., a woman's age, certain sperm problems, genetic background of both parents) may also be associated with an increased chance of birth defects.

#### Pregnancy complications

If treatment with Elonva results in pregnancy, there is a higher chance of pregnancy outside the uterus (an ectopic pregnancy). Therefore, your doctor should perform an early ultrasound examination to exclude the possibility of pregnancy outside the uterus.

#### Ovarian and other reproductive system tumours

There have been reports of ovarian and other reproductive system tumours in women who have had infertility treatment. It is not known if treatment with fertility medicines increases the risk of these tumours in infertile women.

#### Other medical conditions

In addition, before starting to use this medicine, tell your doctor if you:

- have kidney disease.
- have uncontrolled pituitary gland or hypothalamic problems.
- have an underactive thyroid gland (hypothyroidism).
- have adrenal glands that are not working properly (adrenocortical insufficiency).
- have high prolactin levels in the blood (hyperprolactinemia).
- have any other medical conditions (for example, diabetes, heart disease, or any other long-term disease).
- have been told by a doctor that pregnancy would be dangerous for you.

#### **Other medicines and Elonva**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

If you do a pregnancy test during your infertility treatment with Elonva, the test might wrongly suggest that you are pregnant. Your doctor will advise you at what time you can start performing pregnancy tests. In case of a positive pregnancy test, contact your doctor.

#### **Pregnancy and breast-feeding**

You should not use Elonva if you are already pregnant, or think that you might be pregnant, or if you are breast-feeding.

Ask your doctor or pharmacist for advice before taking this medicine.

#### **Driving and using machines**

Elonva may cause dizziness. If you feel dizzy, you should not drive or use machines.

#### **Elonva contains sodium**

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

### 3. How to use Elonva

Always use Elonva exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

#### In women

Elonva is used in women having infertility treatment like *in vitro* fertilisation (IVF). During this treatment, Elonva is used in combination with a medicine (so called GnRH-antagonist) to prevent your ovary from releasing an egg too early. Treatment with the GnRH-antagonist usually starts 5 to 6 days after the injection of Elonva.

The use of Elonva in combination with a GnRH agonist (another medicine to prevent your ovary from releasing an egg too early) is not recommended.

#### In adolescent males (14 years and older)

Elonva in combination with a medicine called hCG, is used for treatment of delayed puberty due to HH. Elonva should be administered once every two weeks, in the morning on the same day of the week.

#### **Dose**

##### Women

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

During the first seven days after the injection with Elonva, you should not use (recombinant) Follicle Stimulating Hormone ((rec)FSH). Seven days after the injection of Elonva, your doctor may decide to continue your stimulation cycle with another gonadotropic hormone, like (rec)FSH. This may be continued for a few days until enough follicles of adequate size are present. This can be checked by ultrasound examination. Treatment with (rec)FSH is then stopped and the eggs are matured by giving hCG (human Chorionic Gonadotropin). The eggs are collected from the ovary 34-36 hours later.

#### In adolescent males (14 years and older)

The dose of Elonva is based on body weight:

##### For adolescent males weighing less than or equal to 60 kg

- 100 micrograms of Elonva once every two weeks for 12 weeks, followed by administration of Elonva (once every 2 weeks) with hCG. If your body weight increases to greater than 60 kg during treatment, your doctor may increase your dose of Elonva to 150 micrograms.

For adolescent males weighing more than 60 kg

- 150 micrograms of Elonva once every two weeks for 12 weeks, followed by administration of Elonva (once every 2 weeks) with hCG.

The combination therapy with hCG twice weekly (500 – 5000 IU) may be necessary for 52 weeks or longer to achieve adult gonadal development.

### **How Elonva is given**

Treatment with Elonva should be supervised by a physician experienced in the treatment of fertility problems. Elonva must be injected under the skin (subcutaneously) into a skin fold (that you pinch between your thumb and index finger), preferably just below the navel. The injection may be given by a healthcare professional (for example a nurse), your partner or yourself, if carefully instructed by your doctor. Always use Elonva exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure. A step-by-step “instructions for use” is given at the end of this leaflet.

Do not inject Elonva into a muscle.

Elonva is supplied in pre-filled syringes that have an automatic safety system to help prevent needle stick injuries after use.

### **If you use more Elonva or (rec)FSH than you should**

If you think you have used more Elonva or (rec)FSH than you should, contact your doctor immediately.

### **If you forget to use Elonva**

If you forgot to inject Elonva on the day you should have, contact your doctor immediately. Do not inject Elonva without talking with your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

### **Serious side effects**

A possible complication of treatment with gonadotropic hormones like Elonva is unwanted overstimulation of the ovaries. The chance of having this complication can be reduced by carefully monitoring the number of maturing follicles. Your doctor will do ultrasound scans of your ovaries to carefully monitor the number of maturing follicles. Your doctor may also check blood hormone levels. The first symptoms of ovarian overstimulation may be noticed as pain in the stomach (abdomen), feeling sick or diarrhoea. Ovarian overstimulation may develop into a medical condition called ovarian hyperstimulation syndrome (OHSS), which can be a serious medical problem. In more severe cases this may lead to enlargement of the ovaries, collection of fluid in the abdomen and/or chest (which may cause sudden weight gain due to fluid buildup) or clots in the blood vessels. Contact your doctor without delay if you have pain in the stomach (abdomen) or any of the other symptoms of ovarian hyperstimulation, even if they occur some days after the injection has been given.

The chance of having a side effect is described by the following categories:

### **Common (may affect up to 1 in 10 women)**

- Ovarian hyperstimulation syndrome (OHSS)
- Pelvic pain
- Feeling sick (nausea)

- Headache
- Pelvic discomfort
- Breast tenderness
- Tiredness (fatigue)

**Uncommon ( may affect up to 1 in 100 women)**

- Twisting of an ovary (ovarian torsion)
- Liver enzyme increases
- Miscarriage
- Pain after oocyte retrieval
- Procedural pain
- Releasing an egg too early (premature ovulation)
- Abdominal distension
- Vomiting
- Diarrhoea
- Constipation
- Back pain
- Breast pain
- Bruising or pain at the injection site
- Irritability
- Mood swings
- Dizziness
- Hot flush

**Not known (cannot be estimated from available data)**

- Allergic reactions (hypersensitivity reactions, both local and generalised, including rash).

Pregnancy outside the uterus (an ectopic pregnancy) and multiple pregnancies have also been reported. These side effects are not considered to be related to the use of Elonva, but to Assisted Reproductive Technology (ART) or subsequent pregnancy.

In rare instances, blood clots (thrombosis) that formed inside a blood vessel, broke off, and travelled inside the bloodstream to block another blood vessel (thromboembolism) have been associated with Elonva therapy as with other gonadotropins.

*If you are an adolescent male*

**Side effects reported in adolescent males:**

**Common (may affect up to 1 in 10 males)**

- Vomiting
- Injection site pain
- Hot flush

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## **5. How to store Elonva**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and outer carton after “EXP” (expiry date). The expiry date refers to the last day of that month.



**Storage by the pharmacist**

Store in a refrigerator (2°C-8°C). Do not freeze.

**Storage by the patient**

There are two options:

1. Store in a refrigerator (2°C-8°C). Do not freeze.
2. Store at or below 25°C for a period of not more than one month. Make a note of when you start storing the product out of the refrigerator, and use it within one month of that date.

Keep the syringe in the outer carton in order to protect from light.

**Do not use Elonva**

- if it has been stored out of the refrigerator for more than one month.
- if it has been stored out of the refrigerator at a temperature of more than 25°C.
- if you notice that the solution is not clear.
- if you notice that the syringe or the needle is damaged.

Do not throw away an empty or unused syringe via household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

**6. Contents of the pack and other information****What Elonva contains**

- The active substance is corifollitropin alfa. Each Elonva 100 micrograms solution for injection pre-filled syringe contains 100 micrograms in 0.5 millilitre (mL) solution for injection. Each Elonva 150 micrograms solution for injection pre-filled syringe contains 150 micrograms in 0.5 millilitre (mL) solution for injection.
- The other ingredients are: sodium citrate, sucrose, polysorbate 20, methionine and water for injections. The pH may have been adjusted with sodium hydroxide and/or hydrochloric acid.

**What Elonva looks like and contents of the pack**

Elonva is a clear and colourless aqueous solution for injection (injection) in a pre-filled syringe with an automatic safety system, which prevents needle stick injuries after use. The syringe is packed together with a sterile injection needle. Each syringe contains 0.5 mL solution.

One pre-filled syringe is available in a single pack.

Elonva is available in two strengths: 100 micrograms and 150 micrograms solution for injection.

**Marketing Authorisation Holder and Manufacturer**

N.V. Organon  
Kloosterstraat 6  
5349 AB Oss  
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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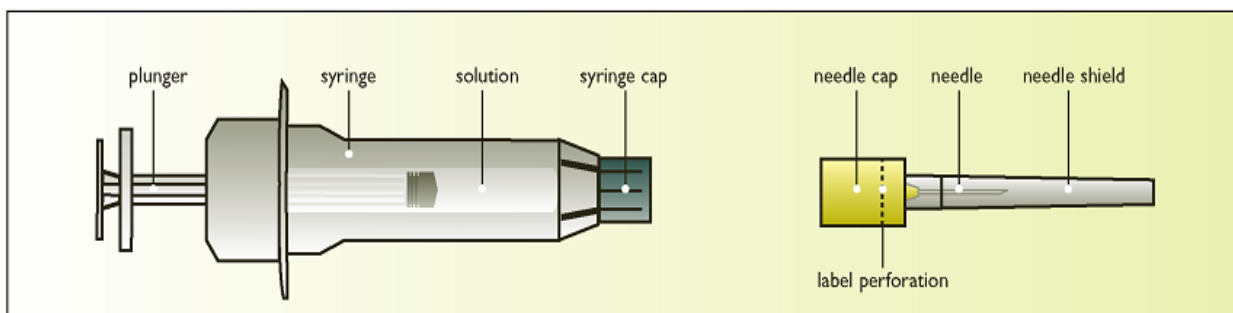
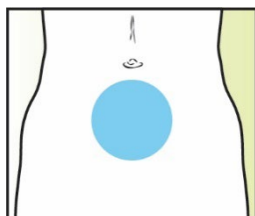
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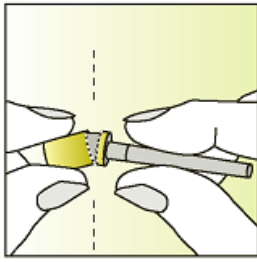
**This leaflet was last revised in Month YYYY.**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

**Instructions for use****Components of the Elonva syringe with needle****Preparing the injection**

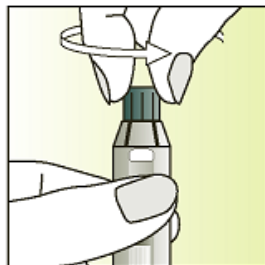
1.
  - Wash your hands with soap and water and dry them before you use Elonva.
  - Swab the injection site (the area just below your belly button) with a disinfectant (for example, alcohol) to remove any surface bacteria.
  - Clean about 5 cm around the point where the needle will go in and let the disinfectant dry for at least one minute before proceeding.



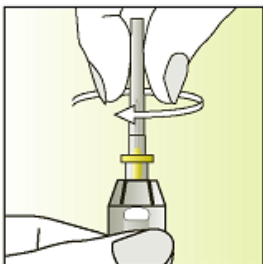
- 2.
- While waiting for the disinfectant to dry, break the label perforation and pull off the needle-cap
  - Leave the needle shield on the needle
  - Place the needle shield (containing the needle) on a clean dry surface, while preparing the syringe.



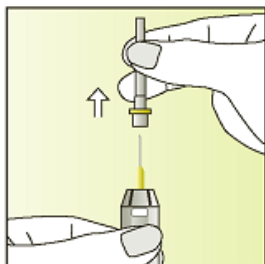
- 3.
- Hold the syringe with the grey cap pointing upwards
  - Tap the syringe gently with your finger to help air bubbles rise to the top.



- 4.
- Keep the syringe pointing upwards
  - Unscrew the syringe cap counter-clockwise.

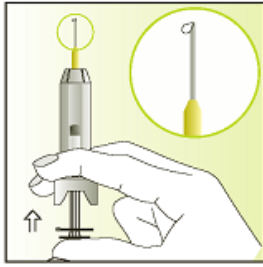


- 5.
- Keep the syringe pointing upwards
  - Screw the needle shield (containing the needle) clockwise onto the syringe.



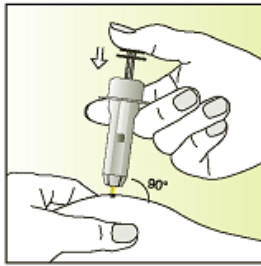
- 6.
- Keep the syringe pointing upwards
  - Remove the needle shield straight up and discard it
  - **BE CAREFUL** with the needle.

## Injecting



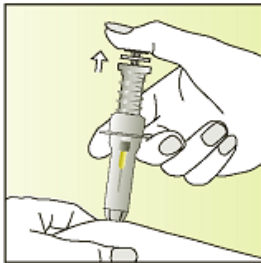
7.

- Now take the syringe between index and middle finger in the upward position
- Place your thumb on the plunger
- Carefully push the plunger upwards until a tiny droplet appears at the tip of the needle.



8.

- Pinch a fold of the skin between thumb and index finger
- Insert the entire needle at an angle of 90 degrees into the fold of the skin
- CAREFULLY press the plunger until it cannot go further and hold the plunger down
- COUNT TO FIVE to ensure that all of the solution is injected.



9.

- Release your thumb from the plunger
- The needle will withdraw automatically into the syringe where it will be locked permanently.