ELONVA®

Corifollitropin alfa (rch)

NAME OF THE DRUG

Corifollitropin alfa solution for injection.

Corifollitropin alfa, a gonadotrophin designed as a sustained follicle stimulant is a glycoprotein consisting of two non-covalently linked non-identical subunits called α and β. The α-subunit is identical to that of human follicle-stimulating hormone (FSH); the β-subunit is composed of the complete β-subunit of human FSH (residues 1-111) extended with the carboxy-terminal peptide (CTP) of the β-subunit of human chorionic gonadotrophin (hCG) (residues 118-145). *CAS No.:* 195962-23-3.

α-subunit

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APDVQDCPEC TLQENPFFSQ PGAPILQCMG CCFSRAYPTP
            *                           *
LRSKKTMLVQ KNVTSESTCC VAKSYNRVTV MGGFKVENHT

ACHCSTCYYH KS
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β-subunit

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      *                   *
NSCELTNITI AIEKEECRFC ISINTTWCAG YCYTRDLVYK

DPARPKIQKT CTFKELVYET VRVPGCAHHA DSLYTYPVAT
                                      &&
QCHCGKCDSD STDCTVRGLG PSYCSFGEMK ESSSSKAPPP
&     &       & &
SLPSPSRLPG PSDTPILPQ
```

* = N-glycosylation sites

& = O-glycosylation sites

Corifollitropin alfa is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology, using a chemically defined cell culture medium without the addition of antibiotics, human- or animal-derived proteins (protein-free) or any other components of human or animal origin.

DESCRIPTION

ELONVA is presented as a sterile, ready for use, clear and colourless aqueous solution for subcutaneous administration. Each pre-filled syringe contains 100 micrograms or 150 micrograms of corifollitropin alfa in 0.5 mL. ELONVA also contains the excipients sodium citrate, sucrose, polysorbate 20, methionine, sodium hydroxide and/or hydrochloric acid (for pH adjustment) and Water for Injections.

ELONVA contains less than 1 mmol sodium (23 mg) per injection, i.e. essentially ‘sodium-free’.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic Group: gonadotrophins

ATC code: G03GA09 corifollitropin alfa.

Corifollitropin alfa has the same pharmacodynamic profile as (rec)FSH, but with a markedly prolonged duration of FSH activity due to a relatively long elimination half-life. This was achieved by the addition of the carboxy-terminal peptide (CTP) of the beta-subunit of hCG to the beta-chain of human FSH. 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. Corifollitropin alfa does not display any intrinsic luteinising hormone (LH)/hCG activity.

Pharmacokinetics

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. Therefore, a single subcutaneous injection of ELONVA may be used as an alternative to the first seven days of daily ref(FSH) in COS for the development of multiple follicles and pregnancy in women undergoing *in vitro* fertilisation techniques (see DOSAGE AND ADMINISTRATION).

Body weight is a determinant of exposure to corifollitropin alfa. The mean corifollitropin alfa exposure (AUC) after a single subcutaneous injection is 665 hours*ng/mL (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. [[1]Predicted range for 90% of subjects.].

Absorption

After a single subcutaneous injection of ELONVA, the mean maximum serum concentration (C_{max}) of corifollitropin alfa is 4.24 ng/mL (2.49 - 7.21 ng/mL[1]) and is reached at the mean T_{max} of 44 hours (35 - 57 hours[1]) postdose. The absolute bioavailability is 58% (48 - 70%[1]). [[1]Predicted range for 90% of subjects.].

Distribution

Distribution, metabolism and elimination of corifollitropin alfa are very similar to other gonadotrophins, such as FSH, hCG and LH. After absorption into the blood, corifollitropin alfa is distributed mainly to the ovaries and the kidneys. Elimination of corifollitropin alfa predominantly occurs via 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. [[1]Predicted range for 90% of subjects.].

Elimination

Corifollitropin alfa has a mean elimination half-life ($t_{1/2}$) 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 PRECAUTIONS and DOSAGE AND ADMINISTRATION). [[1]Predicted range for 90% of subjects.].

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.

CLINICAL TRIALS

In three randomised, double-blind, clinical trials (ENSURE, ENGAGE, and PURSUE), 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 of 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 pregnancy results from the 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	%
FTET Cycle 1[a]												
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 2[a]												
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
FTET Cycle 3[a]												
Ongoing pregnancy	1	9	11.1	0	4	0.0	2	5	40.0	1	4	25.0
Live birth	-	-	-	-	-	-	2	5	40.0	1	4	25.0
FTET Cycle 4[a]												
Ongoing pregnancy	0	3	0.0	0	1	0.0	0	1	0.0	2	2	100.0
Live birth	-	-	-	-	-	-	0	1	0.0	2	2	100.0
FTET Cycle 5[a]												
Ongoing pregnancy	0	2	0.0	0	1	0.0	-	-	-	-	-	-
Live birth	-	-	-	-	-	-	-	-	-	-	-	-

n = number of subjects with the event; N = total number of subjects

[a] Per embryo transfer.

Pregnancy from the addition of FTET cycles to the fresh cycles of ENGAGE and PURSUE (Cumulative Vital Pregnancy Rates)

The cumulative vital pregnancy rate (per subject and per cycle) was calculated based on the results of the fresh and subsequent FTET cycles of a single cohort of women who received ELONVA or recFSH in ENGAGE or PURSUE.

The cumulative vital pregnancy rate from ENGAGE in subjects treated with a single injection of 150 µg ELONVA was similar to that in subjects treated with daily 200 IU recFSH.

The cumulative vital pregnancy rate from PURSUE in subjects treated with a single injection of 150 µg ELONVA was similar to that in subjects treated with daily 300 IU recFSH.

The pregnancy results are summarised in Table 4 below.

Table 4: Pregnancy Results

from fresh ART cycles combined with FTET cycles of ENGAGE and PURSUE

Intent-to-Treat Population (ITT)

Parameter	**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 150 µg	**recFSH 200 IU**	**ELONVA 150 µg**	**recFSH 300 IU**
Cumulative vital pregnancy rate per subject†	N=756	N=750	N=694	N=696
	48.1%	46.0%	31.1%	33.0%
Cumulative vital pregnancy rate per cycle‡	Nc=980	Nc=974	Nc=875	Nc=861
	37.7%	35.8%	25.6%	28.0%

N=Number of subjects
Nc=Number of cycles
†The cumulative vital pregnancy rate was calculated per subject and is based on fresh and frozen-thawed embryo transfer (FTET) cycles from ENGAGE and PURSUE.
‡The cumulative vital pregnancy rate was calculated per cycle and is based on fresh and frozen-thawed embryo transfer (FTET) cycles from ENGAGE and PURSUE.

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-neutralising 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-neutralising antibodies after stimulation with ELONVA is not clinically relevant.

Cardiac Electrophysiology

In a randomized, double-blind, placebo- and active-controlled, 4-period crossover study, 70 healthy postmenopausal women received a single therapeutic dose of 150 mcg of corifollitropin alfa subcutaneously, a single supratherapeutic dose of 240 mcg of corifollitropin alfa subcutaneously, 400 mg moxifloxacin orally, and placebo. Both doses of corifollitropin alfa did not appear to prolong the QTc interval for up to 216 hours postdose. After baseline and placebo adjustment, the maximum mean QTc interval change after administration of a therapeutic dose of 150 mcg of corifollitropin alfa was 1.4 msec (1-sided 95% upper CI: 3.4 msec). After administration of the supratheraeutic dose of 240 mcg of corifollitropin alfa, the maximum mean QTc interval change was 1.2 msec (1-sided 95% upper CI: 3.6 msec).

INDICATIONS

Controlled ovarian stimulation (COS) for the development of multiple follicles and pregnancy in women undergoing *in-vitro* fertilisation techniques.

CONTRAINDICATIONS

- 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.
- A history of Ovarian Hyperstimulation Syndrome (OHSS).
- A previous COS cycle that resulted in more than 30 follicles ≥ 11 mm measured by ultrasound examination.
- A basal antral follicle count > 20.
- Fibroid tumours of the uterus incompatible with pregnancy.
- Malformations of the reproductive organs incompatible with pregnancy.
- Pregnancy or lactation (see PRECAUTIONS).
- Polycystic ovarian syndrome (PCOS).
- Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

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 DOSAGE AND ADMINISTRATION).
- After administration of ELONVA, no additional FSH-containing product should be administered prior to stimulation day 8 (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency

- In patients with renal insufficiency the rate of elimination of corifollitropin alfa may be reduced. Therefore, the use of ELONVA in these women is not recommended (see DOSAGE AND ADMINISTRATION and Pharmacokinetics).

Not Recommended with a GnRH Agonist Protocol

- There are limited data on the use of ELONVA in combination with a Gonadotrophin Releasing Hormone (GnRH) agonist. Therefore, the use of ELONVA is not recommended in combination with a GnRH agonist (see DOSAGE AND ADMINISTRATION).

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 human Chorionic Gonadotrophin (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 gonadotrophin 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 during or 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.

  To reduce 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 estradiol 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. When there are 30 or more follicles in total it is advised to withhold hCG administration.

  Depending on the ovarian response, the following measures can be considered to reduce the risk of OHSS:

  - withhold further stimulation with a gonadotrophin for a maximum of 3 days (coasting);

  - withhold hCG and cancel the treatment cycle;

- administer a dose lower than 10,000 IU of urinary hCG for triggering final oocyte maturation, e.g. 5,000 IU urinary hCG or 250 micrograms rec-hCG (which is equivalent to approximately 6,500 IU of urinary hCG);
- cancel the fresh embryo transfer and cryopreserve embryos;
- avoid administration of hCG for luteal phase support.

Adherence to the recommended ELONVA dosage and treatment regimen and careful monitoring of ovarian response is important to reduce the risk of OHSS. If OHSS develops, standard and appropriate management of OHSS should be implemented and followed.

Ovarian Torsion

- Ovarian torsion has been reported after treatment with gonadotrophins, 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.

Multi-foetal Gestation and Birth

- Multiple pregnancies and births have been reported for all gonadotrophin 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 gonadotrophins 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 gonadotrophins, 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 gonadotrophins, including ELONVA may further increase this risk. In these women the benefits of gonadotrophin administration, including ELONVA, need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.

Use in Pregnancy (Category B3)

The use of ELONVA during pregnancy is contraindicated. In case of inadvertent exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of corifollitropin alfa. 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.

Use in lactation

The use of ELONVA during lactation is contraindicated.

Effects on fertility

Corifollitropin alfa administered to rats and rabbits prior to mating did not impair fertility; treatment stimulated the development of multiple follicles.

Carcinogenicity

Long-term carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of corifollitropin alfa.

Genotoxicity

Corifollitropin alfa was not mutagenic or clastogenic in the standard battery of tests.

Effect 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.

INTERACTIONS WITH OTHER MEDICINES

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.

ADVERSE EFFECTS

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

The table below displays the main adverse drug reactions in women treated with ELONVA in clinical trials according to body system and frequency; common (≥1%, <10%), uncommon (≥0.1%, <1%).

Body system	Frequency	Undesirable effect
Psychiatric disorders	Uncommon	Mood swings
Nervous system disorders	Common Uncommon	Headache
		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

There have been post-marketing reports of hypersensitivity reactions, both local and generalised, including rash.

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

DOSAGE AND ADMINISTRATION

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

ELONVA may be administered 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.

Do not use if the solution contains particles or if the solution is not clear.

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.

		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

* Women younger than 35 years of age who weighed more than 90 kilograms were not studied
† Women older than 42 years of age were not studied

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 PRECAUTIONS and CLINICAL TRIALS).

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 Gonadotrophin Releasing Hormone (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 estradiol 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 (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 ultrasonographic assessments 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 Gonadotrophin (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 urinary hCG is administered the same day or the day thereafter to induce final oocyte maturation. In case of an excessive ovarian response, see the recommendation given in PRECAUTIONS 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 maybe reduced in patients with renal insufficiency, the use of ELONVA in these women is not recommended (see PRECAUTIONS and Pharmacokinetics).

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

Incompatibilities

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

OVERDOSAGE

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 PRECAUTIONS). After administration of ELONVA, no additional FSH-containing product should be administered prior to stimulation day 8, as this may also increase the risk of OHSS. For measures to reduce the risk of and manage OHSS see PRECAUTIONS.

PRESENTATION AND STORAGE CONDITIONS

ELONVA 100 micrograms/ 0.5 mL

ELONVA 150 micrograms/ 0.5 mL

ELONVA is supplied in disposable 1 mL luerlock syringes of hydrolytic glass (type I), closed with a rubber plunger and a tip cap. The syringes are packed together with a sterile injection needle.

Pack size: 1 pre-filled syringe equipped with an automatic safety system to prevent needle stick injuries after use.

Store at 2°C to 8°C (Refrigerate. Do not freeze). Keep the syringe in the outer carton. Product is for single use in one patient only. Contains no antimicrobial preservative. Discard any residue. Do not use after the expiry date on the carton.

ELONVA can also be stored below 25°C for up to 1 month. Do not use after this period.

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited

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Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

21 July 2010

DATE OF MOST RECENT AMENDMENT

14 June 2017