HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

22 September 2010

**ELONVA 100 µg/0.5 ml, solution for injection**
**B/1 prefilled syringe + 1 needle (CIP code: 374 590-1)**
**ELONVA 150 µg/0.5 ml, solution for injection**
**B/1 prefilled syringe + 1 needle (CIP code: 374 591-8)**

**Applicant: SCHERING-PLOUGH**

corifollitropin alfa
ATC code: G03GA09

List I
Medicine requiring special monitoring during treatment.
Prescription restricted to doctors specialised in gynaecology, gynaecology-obstetrics or endocrinology and metabolism.

Date of Marketing Authorisation: 25 January 2010

Reason for request: Inclusion on the lists of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

## 1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient
Corifollitropin alfa

### 1.2. Background
Corifollitropin alfa is the first long-acting follicular stimulant. It is a glycoprotein produced by the recombinant DNA technology.

### 1.3. Indication
"Controlled Ovarian Stimulation (COS) in combination with a GnRH antagonist for the development of multiple follicles in women participating in an Assisted Reproductive Technology (ART) program."

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

*Dosage*
In women with a body weight ≤ 60 kilograms a single dose of 100 micrograms should be administered.
In women with a body weight > 60 kilograms a single dose of 150 micrograms should be administered.
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. The recommended doses of ELONVA have only been established in a treatment regimen with a GnRH antagonist.
Stimulation day 5 and 6:
Treatment with a Gonadotropin 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 and/or the amount of circulating oestradiol. The GnRH antagonist is used to prevent premature Luteinising Hormone (LH) surges.
Stimulation day 8:
Seven days after the injection with ELONVA, treatment may be continued with daily injections of (recombinant) Follicle Stimulating Hormone ((rec)FSH) until the criteria for triggering final oocyte maturation (3 follicles ≥ 17 mm) have 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 from 6 to 18 days of treatment is usually sufficient).
As soon as 3 follicles ≥ 17 mm are observed, a single injection of 5,000 up to 10,000 IU hCG is administered the same day or the day thereafter to induce final follicular maturation. In case of an excessive ovarian response, see the recommendations given in section 4.4 in order to minimise the risk of developing ovarian hyperstimulation syndrome (OHSS).

*Special populations*
Renal impairment: No clinical studies have been performed in patients with renal insufficiency. Since the elimination of corifollitropin alfa might be impaired in patients with renal insufficiency, the use of ELONVA in these women is not recommended.

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

*Paediatric population*
The use of ELONVA in the paediatric population is not relevant within the approved indication.

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

## 2. SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification

G : Genito urinary system and sex hormones
G03 : Sex hormones and modulators of the genital system
G03G : Gonadotropins and other ovulation stimulants
G03GA : Gonadotropins
G03GA09 : Corifollitropin alfa

### 2.2. Medicines in the same therapeutic category

2.2.1 Strictly comparable medicines
Not applicable

2.2.2 Not strictly comparable medicines
Gonadotropins indicated for stimulation of multiple follicular development, for daily administration.

FSH activity

| INN (original) | Trade name | Pharmaceutical form | Indication |
|---|---|---|---|
| Follitropin alfa (recombinant) | GONAL-f®<br>75 IU<br>450 IU/0.75 ml<br>1,050 IU/1.75 ml | Powder and solvent for solution for injection, administered by subcutaneous injection | - GONAL-f in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level < 1.2 IU/l.<br>- Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomiphene citrate.<br>- Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer. |
| | GONAL-f®<br>300 IU/0.5 ml<br>450 IU/0.75 ml<br>900 IU/1.5 ml | Solution for injection in prefilled pen, administered by subcutaneous injection | |
| Follitropin beta (recombinant) | PUREGON®<br>50 IU/0.5 ml<br>75 IU/0.5 ml<br>150 IU/0.5 ml<br>300 IU/0.36 ml<br>600 IU/0.72 ml<br>900 IU/1.08 ml | Solution for injection<br>Administered by intramuscular or subcutaneous injection | Puregon is indicated for the treatment of female infertility in the following clinical situations:<br>- Anovulation (including polycystic ovarian syndrome, PCOS) in women who have been unresponsive to treatment with clomifene citrate.<br>- Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs [e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intrafallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)]. |
| Urofollitropin (urinary) | FOSTIMON®<br>150 IU / ml | Powder and solvent in solution for injection in prefilled syringe, administered by subcutaneous injection | - Anovulation (including polycystic ovarian syndrome (PCOS)) in women who have been unresponsive to treatment with clomiphene citrate.<br>- Controlled ovarian hyperstimulation to induce the development of multiple follicles in the context of assisted reproductive technology treatments, such as in-vitro fertilisation (IVF), gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT). |

FSH and LH activity

| INN (hormonal activity - original) | Trade name | Pharmaceutical form | Indication |
|---|---|---|---|
| Menotropin (urinary) | MENOPUR® 75 IU / 75 IU 1 ml | Powder and solvent for solution for injection, administered by subcutaneous or intramuscular injection | - Treatment of sterility where anovulation is the only cause of sterility:<br>anovulation of hypothalamus-pituitary origin;<br>dysovulation ;<br>- Induction of ovulation in the context of assisted reproductive technology (IVF, GIFT, etc.);<br>- Sterility caused by insufficient production of cervical mucus. |

### 2.3. Medicines with a similar therapeutic aim

Not applicable

## 3. ANALYSIS OF AVAILABLE DATA

The pharmaceutical company submitted two randomised double-blind studies versus active comparators (follitropin beta, PUREGON). Both of these studies were carried out in the context of controlled ovarian stimulation with a view to in-vitro fertilisation or intracytoplasmic sperm injection.

### 3.1. Efficacy

3.1.1 ENGAGE study (38819)

Method

Randomised non-inferiority double-blind (double placebo) (1:1) study versus active comparator: PUREGON (recombinant FSH, follitropin beta).

Main inclusion criteria:

- women for whom controlled ovarian stimulation with a view to IVF or ICSI was indicated
- age between 18 and 36
- weight > 60 kg and ≤ 90 kg; body mass index (BMI) between 18 and 32 kg/m$^2$
- normal menstrual cycle 24 to 35 days

Main exclusion criteria:

- history of hyper-response or ovarian hyperstimulation syndrome
- polycystic ovarian syndrome
- antral follicle count > 20
- more than three consecutive failed attempts at IVF or ICSI
- weak or insufficient ovarian response to previous controlled ovarian stimulation
- FSH or LH > 12 IU/l at the start of the follicular phase
- smoked > 5 cigarettes/day
- repeated miscarriages (three or more).

Treatment:

Ovarian stimulation started on the second or third day of the cycle

- ELONVA group: 1 injection of 150 µg on day 1 of stimulation + 1 daily subcutaneous injection of placebo for the first seven days of stimulation.
- PUREGON group: 1 daily subcutaneous injection of 200 IU of PUREGON for the first seven days of stimulation + 1 subcutaneous injection of placebo on day 1 of stimulation.

- The dose of PUREGON (or PUREGON placebo) could be reduced from day six if necessary. Stimulation could be continued after day eight if necessary, using PUREGON at an appropriate dose (maximum 200 IU/d). The investigator could suspend administration of PUREGON for up to three days if it was thought that this would be beneficial. The maximum length of stimulation was 19 days. The stimulation cycle could be interrupted if the response was inadequate or excessive.

Suppression of LH surge: ganirelix (GnRH antagonist), 0.25 mg/d from day five of stimulation until triggering (5,000 or 10,000 IU of urinary hCG)
Triggering criteria: at least 3 follicles of ≥ 17 mm in diameter on ultrasound
Up to two embryos were transferred three to five days after oocyte retrieval.
Progesterone was administered by the vaginal or intramuscular route to support the luteal phase from the day of oocyte retrieval for at least six weeks or until the patient started her period or a pregnancy test with a negative outcome was performed at least 14 days after embryo transfer.

Primary efficacy endpoints:

- number of evolutive pregnancies in each cycle. An evolutive pregnancy was defined by the presence of at least one foetus with cardiac activity confirmed by ultrasound or Doppler scan ten weeks after transfer or, if this data was not available, by the birth of a live child.
- number of retrieved oocytes per cycle (for patients who did not undergo oocyte retrieval, the number of oocytes was 0).

Main secondary endpoints:

- Stimulation characteristics.

Statistics:
The number of subjects required was determined on the basis of two hypotheses:

- non-inferiority margin of 8%: if the lower limit of the 95% confidence interval of the estimated difference in the rates of evolutive pregnancies between the treatment groups was greater than -8%, ELONVA would have to be considered not inferior to PUREGON
- Rate of evolutive pregnancies of 30%

According to these hypotheses, the minimum number of women to be included was 700 per group to achieve a power of 90%.
The rates of evolutive pregnancies were analysed by comparing the treatment groups using a generalised linear model taking account of age (< 32 or ≥ 32) and region (Europe or North America).
For the number of oocytes retrieved, an equivalence test between treatments was carried out, with an equivalence margin for the difference in the number of oocytes retrieved established at -3 to +5 (95% CI). The treatment groups were compared using an age-adjusted ANOVA (<32 vs. ≥32) and the centre.

Results:

Patients included:
In total, 1,509 patients were included. The breakdown is shown in *table 1*.

Table 1: breakdown of patients during the study

| | ELONVA | PUREGON |
|---|---|---|
| Randomised patients (n) | 757 | 752 |
| Patients treated (ITT) (n) | 756 | 750 |
| Patients with no major deviation from the protocol (PP) (n) | 739 | 733 |
| Patients in whom hCG trigger was successful (n) | 733 | 741 |
| Patients undergoing oocyte retrieval (n) | 732 | 742 |
| Patients undergoing embryo transfer (n) | 672 | 704 |

ITT: intention to treat; PP: per protocol.

The main characteristics of patients treated are shown in *table 2*.

Table 2: characteristics of patients treated (ITT):

| | ELONVA n=756 | PUREGON n=750 |
|---|---|---|
| Average age (years) | 31.5 ± 3.3* | 31.5 ± 3.2* |
| Average weight (kg) | 68.8 ± 7.6* | 68.4 ± 7.3* |
| Average BMI (kg/m$^2$) | 24.8 ± 2.8* | 24.8 ± 2.7* |
| Primary infertility, % (n) | 53.3 (403) | 52.4 (393) |
| Length of infertility (years) | 3.3 ± 2.4* | 3.2 ± 2.2* |
| Cause of infertility, % (n) † | | |
| - Male | 51.3 (388) | 46.3 (347) |
| - Tubal | 26.2 (198) | 25.5 (191) |
| - Endometriosis | 14.4 (109) | 15.3 (115) |
| - Unexplained | 25.4 (192) | 29.5 (221) |
| - other | 9 (68) | 7.8 (58) |
| First attempt at IVF, % (n) | 75.3 (569) | 73.6 (552) |

BMI: body mass index; *: standard deviation; †: multiple causes could be related;

Primary efficacy endpoints:
The results are given in *tables 3 and 4.*

Table 3: PP efficacy results

| | ELONVA n=739 | PUREGON n=733 | Estimated difference |
|---|---|---|---|
| Primary endpoint: evolutive pregnancies*per cycle %,(n) | 39.4% (291) | 38.5% (282) | 1.1 [-3.8 ; 6] † |
| Primary co-criterion: average number of oocytes per cycle | 13.7 ± 8.2‡ | 12.6 ± 6.8‡ | 1.2 [0.5 : 2] † |

*: presence of at least one foetus with cardiac activity confirmed by ultrasound or Doppler scan, 10 weeks after transfer or, if this data was not available, by the birth of a live child; †: 95% confidence interval; ‡: standard deviation.

Table 4: ITT efficacy results

| | ELONVA n=756 | PUREGON n=750 | Estimated difference |
|---|---|---|---|
| Primary endpoint: evolutive pregnancies* per cycle %, (n) | 38.9% (294) | 38.1% (286) | 0.9 [-3.9 ; 5.7] † |
| Primary co-criterion: average number of oocytes per cycle | 13.7 ± 8.2‡ | 12.5 ± 6.7‡ | 1.2 [0.5 : 1.9] † |

* : presence of at least one fœtus with cardiac activity confirmed by ultrasound or Doppler scan, 10 weeks after transfer or, if this data is not available, by the birth of a live child; †: 95% confidence interval; ‡: standard deviation.

As the lower limit of the 95% confidence interval of the estimated difference in the rates of evolutive pregnancies per cycle (ELONVA-PUREGON) was found to be greater than -8% in the per-protocol analysis, ELONVA was considered not inferior to PUREGON in respect of the percentage of evolutive pregnancies per cycle.
As the confidence interval of the estimated difference in the average number of oocytes retrieved per cycle was within the equivalence interval, ELONVA was considered equivalent to PUREGON for this criterion.

Secondary endpoints:
The results are given in *table 5.*

Table 5: characteristics of stimulation

| | ELONVA n=733* | PUREGON n=741* |
|---|---|---|
| Dose of PUREGON (IU) from day 8 to trigger † | 400 (0-2,000) | 400(0-1,400) |
| Total length of stimulation † | 9 (6 - 18) | 9 (6 -15) |

* : patients who received hCG; †: median, min-max;

3.1.2 ENSURE study (107012)

Method
Randomised equivalence double-blind (double placebo) (2:1) study versus active comparator: PUREGON (recombinant FSH, follitropin beta).

Main inclusion criteria:
- women for whom controlled ovarian stimulation with a view to IVF or ICSI was indicated
- age between 18 and 36
- weight ≤ 60 kg; body mass index (BMI) between 18 and 32 kg/$m^2$
- normal menstrual cycle 24 to 35 days.

Main exclusion criteria:
- history of hyper-response or ovarian hyperstimulation syndrome
- polycystic ovarian syndrome
- antral follicle count > 20
- more than three consecutive attempts at IVF or ICSI failed
- weak or insufficient ovarian response to previous controlled ovarian stimulation
- FSH or LH > 12 IU/l at the start of the follicular phase
- smoked > 5 cigarettes/day
- repeated miscarriages (three or more).

Treatment:
The treatment regimen was similar to that followed in the ENGAGE study.
The only difference was in the doses of ELONVA (1 injection of 100 µg) and PUREGON (150 IU/day for the first seven days).

Primary efficacy endpoint:
Number of oocytes retrieved per cycle started.

Main secondary endpoints:
Stimulation characteristics.

Statistics:
Equivalence between the two treatments was considered to have been established if the confidence interval of the estimated difference in the average number of oocytes per cycle was within the predetermined equivalence interval of -3 to +5.

A total of 330 patients were required: 220 in the ELONVA group and 110 in the PUREGON group.
The treatment groups were compared using an age-adjusted ANOVA (<32 vs. ≥32), the fertilisation procedure used (IVF or ICSI) and the centre.

Results:

Patients included:
In total, 396 patients were included. The breakdown is shown in *table 6*.

Table 6: breakdown of patients during the study

| | ELONVA | PUREGON |
|---|---|---|
| Randomised patients (n) | 268 | 128 |
| Patients treated (ITT) (n) | 268 | 128 |
| Patients in whom hCG trigger was successful (n) | 266 | 127 |
| Patients undergoing oocyte retrieval (n) | 266 | 127 |
| Patients undergoing embryo transfer (n) | 246 | 121 |

None of the patients stopped treatment because of an adverse event or had a major deviation from the protocol. The ITT and per-protocol populations are therefore identical.

The main characteristics of patients included are shown in *table 7*.

Table 7: characteristics of patients included

| | ELONVA n=268 | PUREGON n=128 |
|---|---|---|
| Average age (years) | 30.9 ± 3.2* | 31.1 ± 3.0* |
| Average weight (kg) | 54.1 ± 4.2* | 54.4 ± 4.2* |
| Average BMI (kg/m$^2$) | 20.5 ± 1.5* | 20.6 ± 1.6* |
| Primary infertility, % (n) | 60.8 (163) | 64.1 (82) |
| Average length of infertility (years) | 3.2 ± 2.2* | 3.3 ± 2.1* |
| Cause of infertility, % (n) † | | |
| - Male | 47.4 (127) | 53.9 (69) |
| - Tubal | 26.1 (70) | 24.2 (31) |
| - Endometriosis | 11.9 (32) | 8.6 (11) |
| - Unexplained | 27.6 (74) | 25.8 (33) |
| - other | 3.7 (10) | 2.4 (3) |
| First attempt at IVF, % (n) | 55.2 (148) | 60.2 (77) |

BMI: body mass index; *: standard deviation; †: multiple causes may be related;

Primary efficacy endpoint:
The results for the number of oocytes retrieved for each cycle started are given in *table 8*.

Table 8: PP and ITT efficacy results

| | ELONVA n=268 | PUREGON n=128 | Estimated difference |
|---|---|---|---|
| average number of oocytes per cycle | 13.3 ± 7.3* | 10.6 ± 5.9* | 2.5 [1.2 :3.9] † |

* : standard deviation; †: 95% confidence interval

As the confidence interval of the estimated difference in the average number of oocytes retrieved per cycle was within the equivalence interval, ELONVA was considered equivalent to PUREGON for this criterion.

Main secondary endpoints:
The results for the main secondary endpoints are given in *table 9*.
Table 9: characteristics of stimulation

| | ELONVA n=266* | PUREGON n=127* |
|---|---|---|
| Dose of PUREGON (IU) from day 8 to trigger † | 300 (0-1,550) | 275(0-1,600) |
| Total length of stimulation † | 9 (6 - 15) | 9 (6 -15) |
| Patients in whom trigger occurred before or on D8, % (n) | 32.8 (88) | 39.8 (51) |

* : patients who received hCG; †: median and range;

## 3.2. Adverse effects

### 3.2.1 ENGAGE study (38819)

The adverse events recorded during the study are shown in *table 10*.
Table 10: adverse events during the study

| | ELONVA n=755* | PUREGON n=751* |
|---|---|---|
| Patients experiencing at least one AE (%, n) | 63.7% (481) | 61.1% (459) |
| Patients experiencing at least one severe AE (%, n) | 7.3% (55) | 5.7% (43) |
| Patients experiencing at least one major AE (%, n) | 4.5% (34) | 3.7% (28) |
| AE-related study withdrawals (%, n)† | 2.1% (16) | 0.4% (3) |
| Patients experiencing at least one adverse effect (%, n)‡ | 23.4% (177) | 24.9% (187) |

* 1 patient randomised to the PUREGON group was treated with ELONVA and 2 patients randomised to the ELONVA group were treated with PUREGON. For the tolerance analysis they were included in the group for the treatment they received; AE: adverse event; †: including 12 cases of ovarian hyperstimulation syndrome in the ELONVA group and 1 in the PUREGON group; ‡: link to treatment regarded by the investigator as certain, probable or possible.

The most commonly occurring adverse events were:
- headaches/migraines: 10.5% in the ELONVA group vs. 15.2% in the PUREGON group;
- nausea: 9.7% vs. 10.9%;
- pelvic pain: 12.1% vs. 12.3%;
- “pelvic discomfort”: 11.5% vs. 11.6%

The most commonly occurring adverse effects were: “pelvic discomfort” (8.2% vs. 8.3%), headaches (5.0% vs. 7.3%), pelvic pain (6.1% vs. 5.5%) and fatigue (2.6% vs. 2.3%).
Ovarian hyperstimulation syndrome was observed in 7% of patients in the ELONVA group versus 6.3% in the PUREGON group. This was moderate to severe in 3.9% versus 2.5% of cases, and led to withdrawal from the study in 1.6% versus 0.1% of cases.

### 3.2.2 ENSURE study (107012)

The adverse events recorded during the study are shown in *table 11*.

Table 11: adverse events during the study

| | ELONVA n=268* | PUREGON n=128* |
|---|---|---|
| Patients experiencing at least one AE (%, n) | 55.2% (148) | 53.5% (69) |
| Patients experiencing at least one severe AE (%, n) | 3 % (8) | 4.7% (6) |
| Patients experiencing at least one major AE (%, n) | 7.5% (20) | 6.2% (8) |
| AE-related study withdrawals (%, n)† | 0 | 0 |
| Patients experiencing at least one adverse effect (%, n) † | 20.9% (56) | 24.8% (32) |

AE: adverse event; *: one unrandomised patient was treated with PUREGON; †: link to treatment regarded by the investigator as certain, probable or possible.

The most commonly occurring adverse events were:

- "pelvic discomfort": 10.1% in the ELONVA group vs. 14.7% in the PUREGON group;
- pelvic pain: 10.4% vs. 10.9%;
- headaches: 8.2% vs. 8.5%

Ovarian hyperstimulation syndrome was observed in 6.7% of patients in the ELONVA group versus 4.7% in the PUREGON group. This was moderate to severe in 3.4% versus 1.6% of cases, and led to hospitalisation in seven cases (2.6%) in the ELONVA group versus 0 in the PUREGON group.

### 3.3. Conclusion

ELONVA was compared to PUREGON in two randomised double-blind studies.
In one study of 1,509 women, ELONVA was not inferior to PUREGON (at the initial dose of 200 IU) in respect of the percentage of evolutive pregnancies per cycle: 39.4% vs. 38.5%, estimated difference: 1.1 [95% CI: -3.8; 6]
In two studies, the first carried out on 1,509 women and the second on 396 women, ELONVA was equivalent to PUREGON (initial dose of 200 IU in the first study, 150 IU in the second study) in respect of the average number of oocytes retrieved per cycle: 13.7 ± 8.2 vs. 12.6 ± 6.8, estimated difference 1.2 [95% CI: 0.5: 2] in one, 13.3 ± 7.3 vs. 10.6 ± 5.9, estimated difference: 2.5 [95% CI: 1.2: 3.9] in the other.

The incidence of ovarian hyperstimulation syndrome was higher in women being treated with ELONVA compared to those being treated with PUREGON; women with a history of ovarian hyperstimulation or hyper-response had been excluded from the PUREGON group. Consequently, the product is indicated in combination with a GnRH antagonist, and the SPC specifies that ELONVA is contraindicated in patients with a history of ovarian hyperstimulation, who have undergone prior stimulation leading to more than 30 follicles with a diameter of >11mm, or with an antral follicle count of >20, and that it is not recommended for use in combination with a GnRH agonist or in women with polycystic ovarian syndrome[1].
Moderate to severe ovarian hyperstimulation syndrome was observed in 3.9% of women being treated with ELONVA versus 2.5% of those being treated with PUREGON in the first study and 3.4% versus 1.6% in the second study.

1 EPAR for ELONVA : http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001106/WC500074789.pdf

## 4. TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Infertility has a profoundly damaging effect on couples' quality of life.
The proprietary products fall under the category of curative treatment.
The efficacy/adverse effects ratio is high in the population matching the population which took part in clinical studies, i.e. excluding patients at risk of ovarian hyperstimulation because of a history of ovarian hyperstimulation syndrome or hyper-response, polycystic ovarian syndrome, or antral follicle count of > 20.

Public health benefit
Infertility is not a severe condition, but it does have a profoundly damaging effect on couples' quality of life and can have major psychological consequences.
The public health burden of infertility can be regarded as low.
Improvement in the management of infertility, which ELONVA could help to alleviate, has not been identified as a public health priority, but it is a social need.
In the light of the data obtained from equivalence and non-inferiority studies, and given the alternatives available for controlled ovarian stimulation, ELONVA products are not expected to have any impact in terms of quality of life, despite the ease with which they can be administered by injection.
Consequently, ELONVA products are not expected to have an impact on public health.

These proprietary medicinal products are first-line therapies.
There are treatment alternatives.

The actual benefit of these proprietary products is substantial in the population matching the population which took part in clinical studies, i.e. excluding patients at risk of ovarian hyperstimulation because of a history of ovarian hyperstimulation syndrome or hyper-response, polycystic ovarian syndrome, or antral follicle count of > 20.

### 4.2. Improvement in actual benefit (IAB)

ELONVA does not provide any improvement in actual benefit (IAB V) compared to other gonadotropins indicated for stimulation of multiple follicle growth, including PUREGON, the comparator used in clinical studies.

### 4.3. Therapeutic use

4.3.1 Therapeutic use[2]

The therapeutic strategy must take account of the woman's age, how long infertility has been in existence, associated factors and response to previous treatments.

Administration of ovulation inducers requires specific medical training and appropriate experience. All ovulation inducers, apart from clomiphene citrate, can only be prescribed by the specialists defined in the marketing authorisation.

The use of gonadotropins is recommended in ovulation stimulation which is being conducted with a view to in-vitro fertilisation with or without intracytoplasmic micro-injection of sperm.

2 Ovulation-inducing drugs - gonadotropins - Recommendations - Afssaps - April 2007

Follicle retrieval and embryo transfer during in-vitro fertilisation or related techniques may only be performed by authorised practitioners in a centre that has been approved in accordance with the Decree of December 2006.
GnRH antagonists allow a reduction in the length of treatment, the number of injections and (according to some studies) in the risk of hyperstimulation.

4.3.2 Therapeutic use of the proprietary product
ELONVA is a first-line treatment used to induce the development of multiple follicles in women undergoing assisted reproduction treatment. It must be used in conjunction with a GnRH antagonist and is contraindicated in women with a history of ovarian hyperstimulation, where previous stimulation has led to the production of more than 30 follicles of >11mm in diameter or where the antral follicle count was >20. Its use in women with polycystic ovarian syndrome is not recommended[3].

### 4.4. Target population

According to the French Biomedicine Agency, 52,334 attempts at in-vitro fertilisation (with or without ICSI) were recorded in 2007, and assisted reproduction activity was broadly similar in 2007 to what it had been in previous years[4].
ELONVA is contraindicated for women known to be at risk of ovarian hyperstimulation. According to a survey conducted by the pharmaceutical firm Schering-Plough among 20 doctors practising IVF[5], around 15% of patients were regarded as “hyperresponsive”.

According to these assumptions, the target population of ELONVA relates to approximately 44,500 attempts per year.

### 4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in indication and at dosage in the Marketing Authorisation.

4.5.1 Packaging: Appropriate for the prescription conditions

4.5.2 Reimbursement rate: 100%

3 EPAR for ELONVA : http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001106/WC500074789.pdf
4 French Biomedicine Agency - Report on human procreation and genetics activities in France in 2007
5 Study conducted to assess the IVF/ICSI protocol in France. Pascaléo research institute. Unpublished study - May 2010