AUSTRALIAN PRODUCT INFORMATION - OVALEAP® (follitropin alfa (rch)) solution for injection

1. NAME OF THE MEDICINE

Follitropin alfa (rch)

OVALEAP is a biosimilar medicine to GONAL-f® solution for injection. The evidence for comparability supports the use of OVALEAP for the listed indications.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OVALEAP is produced by a Chinese Hamster Ovary cell line transfected with the human FSH subunit genes (i.e. by recombinant DNA technology). Each cartridge contains the active ingredient follitropin alfa (rch) (recombinant human follicle stimulating hormone) 300 IU/0.5 mL, 450 IU/0.75 mL or 900 IU/1.5 mL.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Solution for injection available in packs containing 1 glass cartridge and 10 or 20 injection needles. The Ovaleap cartridge is designed for use in conjunction with the Ovaleap Pen only, which is separately available.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

1. The treatment of anovulatory infertility in women who have been unresponsive to clomiphene citrate or where clomiphene citrate is contraindicated.
2. For controlled ovarian hyperstimulation in women undergoing assisted reproductive technologies.
3. OVALEAP is indicated with concomitant human chorionic gonadotrophin (hCG) therapy for the stimulation of spermatogenesis in gonadotrophin-deficient men in whom hCG alone is ineffective.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

OVALEAP should be administered subcutaneously. The injection site should be alternated daily to prevent lipoatrophy. Self-administration of OVALEAP should only be performed by patients who are well motivated, adequately trained and who have access to expert advice. Ovaleap cartridge should only be administered using the OVALEAP Pen. The instructions for use of the pen will be provided together with the OVALEAP Pen. Each OVALEAP pen is for individual patient use only.

Women with Anovulatory Infertility (WHO Group II)

The objective of OVALEAP therapy is to develop a single mature Graafian follicle from which the ovum will be liberated after the administration of hCG.

OVALEAP may be given as a course of daily injections. In menstruating patients treatment should commence within the first 7 days of the menstrual cycle. Treatment should be tailored to the individual patient's response as assessed by measuring 1) follicle size by ultrasound and/or 2) oestrogen secretion. A commonly used regimen commences at 75 – 150 IU (5.46 to 10.92 microgram) FSH daily and is increased by 37.5 IU (2.73 microgram) up to 75 IU (5.46 microgram) at 7 or 14 day intervals if necessary, to obtain an adequate, but not excessive response. If a patient fails to respond adequately after 5 weeks of treatment, that cycle should be abandoned.

When an optimal response is obtained, a single injection of 250 microgram r-hCG or 5000 IU up to 10,000 IU urinary human chorionic gonadotropin (u-hCG) should be administered 24 – 48 hours after the last OVALEAP injection. The patient is recommended to have coitus on the day of, and the day following hCG administration.

If an excessive response is obtained, treatment should be stopped and hCG withheld (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Treatment should recommence in the next cycle at a dosage lower than that of the previous cycle.

Women undergoing Assisted Reproductive Technologies

A commonly used regimen for superovulation involves the administration of 150 IU (10.92 microgram) to 225 IU (16.5 microgram) of OVALEAP daily, commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum oestrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450 IU (32.76 microgram) daily.

A single injection of 250 microgram r-hCG or 5000 IU up to 10,000 IU u-hCG is administered 24 – 48 hours after the last OVALEAP injection to induce final follicular maturation. In clinical trials, final follicular maturation was judged to be when at least two follicles were ≥ 16 mm mean diameter and when E2 levels were within the physician’s acceptable range for the number of follicles present.

Down-regulation with either a GnRH agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. Dosage regimens should be customised in order to achieve the desired result. In a commonly used protocol OVALEAP is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks treatment with an agonist, 225 IU (16.5 microgram) OVALEAP is administered (subcutaneously) for the first 7 days. The dose is then adjusted according to the ovarian response.

Men with Hypogonadotrophic Hypogonadism

Prior to combined therapy with OVALEAP and hCG, pre-treatment should begin with hCG alone at the appropriate dosage to achieve masculinisation and serum testosterone level within the eugonadal range (> 9 – 10 nmol/L). This starting dose should be increased to the necessary

dosage in order to obtain normal testosterone values. If after an inadequate trial of hCG alone (usually 6 months) at effective doses, OVALEAP should be given concomitantly at the dosage of 150 IU (10.92 microgram) three times a week. This regimen should be continued for a minimum of 4 months. If after this period, the patient has not responded, the combination treatment (hCG plus OVALEAP 150 IU (10.92 microgram) 3 times a week) may be continued. Current clinical experience indicates that prolonged treatment for up to 18 – 24 months may be necessary to achieve spermatogenesis or fertility.

4.3 CONTRAINDICATIONS

OVALEAP is contraindicated for safety reasons in:

- cases of prior hypersensitivity to follitropin alfa, or to any excipients of OVALEAP
- tumours of the hypothalamus or pituitary gland

FSH therapy is contraindicated for safety reasons where the following exist:

In women:

- pregnancy and lactation
- ovarian enlargement or ovarian cyst of unknown aetiology
- gynaecological haemorrhages of unknown aetiology
- ovarian, uterine or breast carcinoma

FSH is contraindicated when an effective response cannot be obtained, such as:

In women

- primary ovarian failure as indicated by high levels of FSH (ovarian dysgenesis, premature menopause)
- malformations of sexual organs incompatible with pregnancy
- fibroid tumours of the uterus incompatible with pregnancy

In men

- elevated gonadotrophin levels that indicate primary testicular failure
- infertility disorders other than hypogonadotrophic hypogonadism

Use in Elderly and Children

OVALEAP should not be used in the elderly or children.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

OVALEAP is a potent gonadotrophic substance capable of causing mild to severe adverse reactions, and should only be used by physicians who are thoroughly familiar with infertility problems and their management.

Gonadotrophin therapy requires a certain time commitment by physicians and supportive health professionals, as well as the availability of appropriate monitoring facilities. In women, safe and effective use of OVALEAP calls for monitoring of ovarian response with ultrasound,

alone or preferably in combination with measurement of serum oestradiol levels, on a regular basis. There may be a degree of inter-patient variability in response to FSH administration, with a poor response to FSH in some patients and exaggerated response in others. The lowest effective dose in relation to the treatment objective should be used in both men and women.

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinaemia, and appropriate specific treatment given.

OVALEAP should be used with caution in patients with known hypersensitivity to gonadotrophin presentations that do not contain FSH, due to the risk of cross-sensitivity. The first injection of OVALEAP in such patients must be performed under direct medical supervision.

Self-administration of OVALEAP should only be performed by patients who are well motivated, adequately trained and with access to expert advice. During training of the patient for self-administration, special attention should be given to specific instructions for use of the OVALEAP Pen. The instructions for use of the pen will be provided together with the OVALEAP Pen.

Treatment in women

Patients should be selected carefully according to the following guidelines: a thorough gynaecological and endocrinological evaluation must be performed; presence of early pregnancy should be ruled out; aetiology of any abnormal vaginal bleeding should be established before starting OVALEAP therapy; evaluation of semen quality of the partner should be performed; or other appropriate investigations should be performed as required.

Ovarian Hyperstimulation Syndrome (OHSS)

Mild to moderate uncomplicated ovarian enlargement, which may be accompanied by abdominal distension and/or abdominal pain, occurs in approximately 20% of those treated with follitropin and hCG, and generally regresses without treatment within two or three weeks. In the presence of marked ovarian enlargement, treatment should be discontinued.

Patients undergoing superovulation are at an increased risk of developing Ovarian Hyperstimulation Syndrome (OHSS) in view of the excessive oestrogen response and multiple follicular development. Distinct from uncomplicated ovarian enlargement, OHSS is a condition that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.

OHSS can become a serious complication of human gonadotrophin therapy and sometimes leads to fatal complications if not adequately treated.

Mild manifestations of OHSS include abdominal pain, abdominal discomfort and distension, and enlarged ovaries. Moderate OHSS may additionally present with nausea, vomiting, ultrasound evidence of ascites and marked ovarian enlargement. Severe OHSS further includes symptoms such as severe ovarian enlargement, weight gain, dyspnoea or oliguria. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, pleural effusions or

acute pulmonary distress. Rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events, such as pulmonary embolism, ischaemic stroke or myocardial infarction.

Independent risk factors for developing OHSS have been reported to include young age, lean body mass, polycystic ovarian syndrome (PCOS), higher doses of exogenous gonadotrophin high absolute or rapidly rising serum oestradiol levels and previous episodes of OHSS, large number of developing ovarian follicles and large number of oocytes retrieved in ART cycles.

Careful monitoring of ovarian response with ultrasound alone or preferably in combination with measurement of oestradiol levels is recommended prior to and during stimulation therapy, especially in patients with PCOS.

OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event. It most often occurs after treatment with follitropin or hCG has been discontinued, reaching its maximum at about seven to ten days following treatment. Therefore, patients should be followed for at least two weeks after follitropin or hCG administration.

If there are any symptoms or signs of OHSS, the patient must be evaluated, investigated, and monitored. Adherence to recommended OVALEAP dosage and regimen of administration can minimise the risk of OHSS. Monitoring of stimulation cycles by ultrasound scans as well as oestradiol measurements are recommended to identify risk factors early.

Excessive oestrogenic response seldom gives rise to significant hyperstimulation unless hCG is administered to induce ovulation. Cases of OHSS are more common, more severe and more protracted if pregnancy occurs. Therefore, if signs of OHSS occur, it is recommended that hCG be withheld and the physician should advise the patient to refrain from intercourse for at least 4 days. Intercourse should be prohibited in those patients in whom significant ovarian enlargement occurs after ovulation because of the danger of haemoperitoneum resulting from ruptured ovarian cysts.

Mild or moderate OHSS requires careful monitoring and may resolve spontaneously. Worsening of symptoms suggests progression of OHSS and requires prompt clinical reassessment. If necessary, the physician should recommend cessation of treatment or withholding hCG injection, and closely monitor the ovarian response. Severe OHSS requires admission to hospital and commencement of appropriate therapy in addition to cessation of gonadotrophins treatment. Treatment of OHSS is primarily symptomatic, consisting of bed rest, fluid and electrolyte management, and analgesics if needed.

The phenomenon of haemoconcentration associated with fluid loss into the peritoneal cavity, pleural cavity and pericardial cavity has been seen to occur and should be thoroughly assessed in the following manner: 1) fluid intake and output, 2) weight, 3) haematocrit, 4) serum and urinary electrolytes, 5) urine specific gravity, 6) BUN and creatinine, and 7) abdominal girth. These determinations are to be performed daily or more often if the need arises. Appropriate imaging examination, especially ultrasound, should also be used for identifying, localising and quantifying fluid loss.

There is an increased risk of injury to the ovary with OHSS. The ascitic, pleural and pericardial fluids should not be removed unless absolutely necessary to relieve symptoms such as

pulmonary distress or cardiac tamponade. Pelvic examination may cause rupture of an ovarian cyst, which may result in haemoperitoneum and should therefore be avoided. If this does occur, and if bleeding becomes such that surgery is required, the surgical treatment should be designed to control bleeding and to retain as much ovarian tissue as possible.

Thromboembolic events

Thromboembolic events, including thrombophlebitis, pulmonary embolism, stroke and arterial occlusion both in association with, and separate from OHSS, have been reported following gonadotrophin therapy. In rare cases, thromboembolic events have resulted in death.

In women with recent or ongoing thromboembolic disease or women with generally recognised risk factors for thromboembolic events, such as personal or family history, treatment with gonadotrophins may further increase the risk for aggravation or occurrence of such events. In these women, the benefits of gonadotrophin administration need to be weighed against the risks. It should be noted, however, that pregnancy itself, as well as OHSS, also carries an increased risk of thromboembolic events.

Multiple pregnancies

In patients undergoing induction of ovulation, the incidence of multiple pregnancy is increased compared with natural conception. The majority of multiple conceptions are twins. Multiple pregnancies, especially higher order, carry an increased risk of adverse maternal and perinatal outcomes. The patient should be advised of the potential risk of multiple births before starting treatment.

To minimise the risk of twins or higher order multiple pregnancy, careful monitoring of ovarian response is recommended. Appropriate management, such as cycle cancellation, should be considered in line with current clinical practice. The incidence of multiple pregnancy can be minimised by using the recommended dose and schedule of administration (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In patients undergoing ART procedures, the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient's age. Single embryo transfer in good prognosis cycles substantially reduces the risk of multiple pregnancy with little effect on live birth rates.

Pregnancy loss

The incidence of pregnancy loss by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than following natural conception, but comparable with the rates found in women with other fertility problems.

Congenital anomalies

The prevalence of congenital anomalies after the use of ART may be slightly higher than after spontaneous conceptions. Possible contributing factors include aspects inherent in the couple's infertility, ovulation induction agents, other medicines used in treatment and the ART procedures. While there is no specific evidence from clinical trials or post-marketing data implicating gonadotrophin use in adverse effects on pregnancy, embryonal or fetal development, parturition or postnatal development, ovulation induction agents cannot be excluded as a contributing factor.

Treatment in men

Elevated endogenous FSH levels are indicative of primary testicular failure. Such patients are unresponsive to OVALEAP/hCG therapy. Semen analysis is recommended in assessing the response to treatment.

Porphyria

In patients with porphyria or a family history of porphyria, follitropin alfa may increase the risk of an acute attack. Deterioration or a first appearance of this condition may require cessation of treatment.

Use in the elderly

OVALEAP should not be used in the elderly population (see Section 4.3 CONTRAINDICATIONS).

Paediatric use

OVALEAP should not be used in the paediatric population (see Section 4.3 CONTRAINDICATIONS).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinically significant drug interactions have been reported during OVALEAP therapy. Concomitant use of OVALEAP with other agents used to stimulate ovulation may potentiate the follicular response, whereas concurrent use of a GnRH) agonist or antagonist to induce pituitary desensitisation may increase the dosage of OVALEAP needed to elicit an adequate ovarian response.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See Section 4.1 THERAPEUTIC INDICATIONS.

Use in pregnancy – Pregnancy Category D

Follitropin alfa is not intended for use during pregnancy (see Section 4.3 CONTRAINDICATIONS). In rats and rabbits, follitropin alfa caused dystocia and marked postimplantation loss at subcutaneous doses of greater than 5 IU/kg/day, indicating that it is embryotoxic and fetotoxic. Follitropin alfa was not teratogenic at subcutaneous doses up to 320 IU/kg/day in rats or 5 IU/kg/day in rabbits.

Use in lactation.

It is not known whether follitropin alfa is excreted in human milk. In lactating rats, follitropin alfa at doses up to 40 IU/kg did not influence lactation or have any effects on the postnatal growth and development of the offspring. Follitropin alfa was measured in the milk in early lactation.

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in the nursing infant from OVALEAP, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, adverse events of these medicines include dizziness which could affect the ability to drive or use machines (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The reactions reported below are classified according to frequency of occurrence as follows:

Very Common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥ 1/10,000 to < 1/ 1,000
Very Rare	< 1/10,000

Treatment in general

Immune system disorders

Very rare: Mild to severe hypersensitivity reactions including anaphylactic reactions and shock

Respiratory, thoracic and mediastinal disorders

Very rare: Exacerbation or aggravation of asthma

General disorders and administration site conditions

Very common: Injection site reactions (e.g. pain, erythema, haematoma, swelling and/or irritation at the site of injection)

Treatment in women

The following adverse events have been reported during gonadotrophin therapy:

Reproductive system and breast disorders

Very common: Ovarian cyst, mild to moderate ovarian enlargement

Common: Mild or moderate OHSS (including symptomatology), intermenstrual bleeding

Uncommon: Severe OHSS (including symptomatology)

Rare: Complications of severe OHSS, ectopic pregnancy, adnexal torsion associated with ovarian enlargement

Gastrointestinal disorders

Common: Abdominal pain, abdominal distension, abdominal discomfort, diarrhoea, nausea,

vomiting

Nervous system disorders

Very common: Headache, dizziness

Vascular disorders

Rare: Thromboembolism

Refer to PRECAUTIONS for information on symptoms and management of OHSS.

Treatment in men

Reproductive system and breast disorders

Common: Gynaecomastia

Skin and subcutaneous tissue disorders

Common: Acne

Investigations

Common: Weight gain

Reporting suspected adverse reactions
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems

4.9 OVERDOSE

The effects of an overdose of follitropin alfa are unknown, nevertheless, there is the possibility that OHSS may occur (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

In females, the most important effect resulting from parenteral administration of FSH is the development of mature Graafian follicles. To complete follicular maturation and to stimulate ovulation in the absence of an endogenous luteinising hormone (LH) surge, human chorionic gonadotrophin (hCG) is given once monitoring of the patient indicates that sufficient follicular development has occurred. There may be a degree of inter-patient variability in response to FSH administration, with lack of response to FSH in some patients. In males, FSH stimulates spermatogenesis without significant effect on the androgen secreting interstitial cells.

Clinical trials

Clinical Trials with GONAL-f

WHO Group II anovulatory infertile women

In a controlled study involving 222 randomised patients, cumulative ovulation rate was not significantly different between follitropin alfa and urofollitropin or urinary-derived hFSH (u-hFSH) groups whether analysed on an intention-to-treat or evaluable patient basis. The ovulation rate in each cycle was also not different between the two medicines.

Superovulation in Assisted Reproduction Techniques (ART)

Study 21884: The safety and efficacy of follitropin alfa (r-hFSH; filled-by-mass) versus u-hFSH and its equivalence as compared to follitropin alfa old formulation (filled by bioactivity), all administered subcutaneously, were assessed in a multicentre, randomised, single blind, phase III study in infertile women undergoing *in vitro* fertilisation (IVF) and embryo transfer. All patients underwent pituitary desensitisation (down-regulation) with a gonadotrophin-releasing hormone (GnRH) agonist prior to and during stimulation of multiple follicular development with one of the three study treatments. Randomisation occurred when pituitary down-regulation was confirmed by an E_2 level of < 50 pg/mL.

The primary efficacy parameter in this study was the number of fertilised oocytes retrieved per patient. 837 patients entered the study, of whom 713 were randomised. Of these, 711 received at least one dose of FSH: 237 patients received follitropin alfa (r-hFSH; filled-by-mass), 237 patients received u-hFSH, and 237 patients received follitropin alfa old formulation (filled by bioactivity). The number of oocytes retrieved was similar in all treatment groups. The efficacy of follitropin alfa (r-hFSH; filled-by-mass) although not superior, led to statistically higher response rates in the number of fertilised oocytes as compared to u-hFSH. The efficacy results are summarised below in Tables 1 and 2:

Table 1. Number of Oocytes Fertilised: Summary Statistics (mean (sd)) by Treatment (Study 21884)

Number of patients	Missing	r-hFSH (filled-by-mass)	u-hFSH	-hFSH(filled by bioactivity)	Overall
653	29	6.7 (4.1)	6.0 (3.7)	6.1 (4.3)	6.3 (4.0)

Table 2. Number of Oocytes Fertilised: Statistical Comparisons between the Treatment Groups by Age and Type of Insemination

Age	Insemi-nation	r-hFSH (fbm) vs u-hFSH	Estimated difference	90% CI	r-hFSH(fbm) vs old r-hFSH (filled by bioactivity)	Estimated difference	95% CI
< 35	IVF	0.257	0.96	[-0.44, 2.36]	0.471	0.62	[-1.07, 2.30]
	ICSI	0.009	1.45	[0.54, 2.36]	0.004	1.64	[0.54, 2.73]
	All	0.002	1.41	[0.66, 2.16]	0.001	1.52	[0.62, 2.41]
>=35	IVF	0.865	-0.20	[-2.18, 1.77]	0.963	-0.06	[-2.61, 2.49]
	ICSI	0.112	-1.58	[-3.21, 0.06]	0.119	-1.56	[-3.53, 0.41]
	All	0.141	-1.04	[-2.20, 0.12]	0.059	-1.35	[-2.76, 0.05]
All	IVF	0.510	0.43	[-0.65, 1.51]	0.826	0.15	[-1.15, 1.44]
	ICSI	0.098	0.78	[0.00, 1.55]	0.083	0.81	[-0.11, 1.73]
	All	0.052	0.74	[0.11, 1.36]	0.082	0.66	[-0.08, 1.40]

fbm: filled-by-mass

441 of 713 patients experienced 1474 adverse events: 145 patients in the follitropin alfa (r-hFSH; filled-by-mass) group, 143 patients in the u-hFSH group and 153 patients in the old follitropin alfa (filled by bioactivity) group. Most of the reported events were less in the follitropin alfa (r-hFSH; filled-by-mass) group when compared to the old follitropin alfa (filled by bioactivity) group. Overall, the pattern of adverse events was similar between treatment groups and was consistent with the profile of events reported in this indication.

Men with Hypogonadotrophic Hypogonadism

Male hypogonadotrophic hypogonadism (HH) is a rare condition therefore study sizes are limited. Two phase III (open and non-comparative) studies were conducted to assess the efficacy and safety of follitropin alfa in combination with hCG in inducing spermatogenesis in men with HH. The primary efficacy endpoint was the achievement of a mature sperm density of > 1.5 x 10^6/mL. Follitropin alfa was administered subcutaneously at a dosage of 150 IU three times a week in combination with hCG (> 2000 IU twice weekly) for up to 18 months.

The first study was conducted in university clinical centres in France, Germany and UK. A total of 32 patients with complete, primary isolated HH were recruited into this study. They were azoospermic before entering the study, remained so after the pre-treatment phase and none had prior treatment with FSH or GnRH. In the pre-treatment phase, the patients were treated with hCG alone (2000 IU twice weekly for 3 – 6 months) to first normalise serum testosterone levels

before initiating the treatment with follitropin alfa. Of 26 patients who received follitropin alfa, 19 patients were found to be eligible for efficacy evaluation.

The primary endpoint of a sperm density of > 1.5 x 10^6/mL was achieved in 12/19 (63%) patients. Overall 15/19 (79%) patients achieved some spermatogenesis. The median time to initiate spermatogenesis was 9 months.

The second study was conducted in 2 university clinical centres in Australia. A total of 10 patients with severe HH entered the study, but only 8 patients completed the follitropin alfa treatment phase. Similar results to the first study were obtained.

The primary endpoint of a sperm density of > 1.5 x 10^6/mL were achieved in 5/8 (63%) patients. Overall 7/8 (88%) patients achieved some spermatogenesis. The median time to initiate spermatogenesis was 6 months. The studies also demonstrated that follitropin alfa has a good safety profile and is well tolerated over the treatment period of up to 18 months.

Comparability of OVALEAP with Gonal-f
Therapeutic equivalence of OVALEAP and Gonal-f was demonstrated in a multi-national, multi-centre, randomised, controlled, assessor-blind, parallel-group study in women undergoing controlled ovarian hyperstimulation for ART.

The primary efficacy endpoint was the number of oocytes retrieved. Equivalence of OVALEAP and Gonal-f was considered to be shown if the two-sided 0.95 CI for the differences in the number of oocytes retrieved lied entirely within the equivalence range of [-3 oocytes, + 3 oocytes].

Secondary endpoints included total r-hFSH dose and dose adaptation; duration of r-hFSH stimulation; follicle size distribution, serum oestradiol and endometrial thickness on Stimulation Day 6 and on the day of hCG administration; cancellation rate prior to oocyte retrieval; oocyte maturity (ICSI); oocyte quality; fertilisation rate; and clinical pregnancy rate; and confirmed no clinically meaningful differences between OVALEAP and Gonal-f.

5.2 PHARMACOKINETIC PROPERTIES

Following intravenous administration, follitropin alfa is distributed to the extracellular fluid space with an initial half-life of around 2 hours and eliminated from the body with a terminal half-life of about 1 day. The steady state volume of distribution and total clearance are 10 L (0.17 L/kg) and 0.6 L/h (0.01 L/h/kg), respectively. One-eighth of the follitropin alfa dose is excreted in the urine.

Following subcutaneous administration, the absolute bioavailability is about 70%. Following repeated administration, follitropin alfa accumulates 3-fold at steady state within 3 – 4 days. In women whose endogenous gonadotrophin secretion is suppressed, follitropin alfa has nevertheless been shown to effectively stimulate follicular development and steroidogenesis, despite unmeasurable LH levels.

A phase I (study IMP 23572), open, randomised, 2-way crossover study to assess the relative bioavailability and the tolerability of r-hFSH of a reference follitropin alfa as a monodose freeze-dried formulation and a new multidose liquid formulation, administered subcutaneously

in male and pre-menopausal female volunteers with pituitary gonadotrope cell down regulation was conducted. The pharmacokinetic parameters from this study can be seen in Table 3 below.

Table 3. Summary of the statistics (means, point estimate, confidence interval) on pharmacokinetic parameters of r-hFSH by treatment (liquid/test and lyophilised/reference formulation) – Study IMP 23572

Parameter	Test (N = 41)	Reference (N = 40)	Point estimate Ratio test/reference (N = 39)	90% CI range (0.8 – 1.25)
C_{max} (IU/L) (Min – max)	8.99 (4.70 – 16.7)	9.51 (4.00 – 15.1)	0.9175	(0.8855, 0.9505)
AUC_{last} (IU.h/L) (Min – max)	841 (557 – 2280)	844 (462 – 1170)	0.9512	(0.9222, 0.9810)
t_{max} (h)* (Min – max)	15.0 (6.00 – 48.0)	12.0 (4.00 – 48.0)	NA	NA

(*median values for t_{max})

Following the subcutaneous administration of both formulations, the 90% confidence intervals of the mean ratios for the bioavailability metrics, C_{max} and AUC_{last} lie within the pre-defined limits of 0.8 – 1.25 showing bioequivalence of liquid (test) and freeze dried (reference) formulations. Because the observed variability (<10%) was much lower than expected *a priori*, the study allowed the detection of a small difference between the two formulations in rate (about 8%) and extent (about 5%). Suppression of endogenous FSH production was incomplete, probably more so in period 2 compared to period 1 and this probably explains the significant period effect observed. The significant difference seen on t_{max} is probably a function of the diverse mechanisms by which the drug enters the systemic circulation. In subjects where the diffusion processes from the subcutis to the adjacent small blood vessels dominate, earlier t_{max} is observed, whereas, in subjects where flow of FSH through the lymph to the systemic circulation is dominant, a later t_{max} probably occurs. This latter process may be non-linear generating an apparent zero order input over sustained periods in some subjects. The mixture of these processes in the population leads to very high variability in t_{max} so a larger study would be necessary to truly assess the relative magnitude of this parameter for the two formulations.

Comparability of OVALEAP with Gonal-f

Equivalent pharmacokinetic (PK) profiles of OVALEAP and Gonal-f have been demonstrated in a randomised, open label, two-way cross-over phase I study in 36 healthy, down-regulated (suppression of endogenous pituitary gonadotrophin release with a gonadotrophin-releasing hormone (GnRH) agonist prior to stimulation with either Gonal-f or OVALEAP) women. The results of comparative statistical evaluation of the pharmacokinetic parameters are summarized in Table 4.

Table 4 Comparative statistical evaluation: Pharmacokinetic parameters of FSH (pk population and ratios with 90% confidence intervals

Parameter	Units	Ovaleap	Gonal-f®	Ratio with 90% confidence intervals OVALEAP/Gonal-f®
C_{max}	IU/L	9.18 (2.42) (mean SD) min – max 3.42 – 13.99	9.04 (2.49) (mean SD) min-max 4.42-14.44	1.017 (0.958,1.080)
AUC $_{0-t}$	IU*h/L	632.0 (167.1) (mean SD) min – max 175-902	619.2 (191.1) (mean SD) min – max 261 -1131	1.028 (0.931,1.134)
$t_{1/2}$	h	32.8 (11.1) (mean SD) min-max 9.4 - 51.5	33.7 (10.2) (mean SD) min-max 10.5 - 48.4	
t_{max*}	h	19.8 (8.4) (mean SD) min-max 10.0 - 48.0	19.7 (7.9) (mean SD) min-max 10.0 - 36.0	

C_{max} = maximum concentration

AUC_{0-t} = area under the concentration-time curve from time zero to the time of last observed concentration

$t_{1/2}$ = apparent half-life of terminal elimination

t_{max} = time at which Cmax occurred

Log-transformed evaluation (except for tmax), results presented after back-transformation.

Ratios derived from least squares geometric means, for tmax nonparametric estimate of difference.

Individual parameter estimates of insufficient reliability were excluded from the analyses.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Follitropin alfa showed no genotoxic activity in a series of assays performed to evaluate its potential to cause gene mutations (*Salmonella typhimurium*, *Escherichia coli* and Chinese hamster lung cells) and chromosomal damage (human lymphocytes and mouse micronucleus test).

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Monobasic sodium phosphate dihydrate, sodium hydroxide (2 M) (for pH adjustment), mannitol, Methionine, polysorbate 20, benzyl alcohol, benzalkonium chloride and water for

injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG) in Australia. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

Should refrigeration be unavailable, OVALEAP cartridge can be stored below 25°C for up to 3 months. OVALEAP must be discarded if it has not been used after 3 months.

After first using the OVALEAP cartridge with the supplied pen, OVALEAP may be stored below 25°C for a maximum of 28 days. Store the pen with the cap on, in order to protect the product from light.

6.5 NATURE AND CONTENTS OF CONTAINER

OVALEAP is available in the following strengths and pack sizes:

Ovaleap 300 IU/0.5 mL solution for injection

Cartridge (type I glass) with a rubber piston (bromobutyl rubber) and a crimp-cap (aluminium) with a septum (bromobutyl rubber), containing 0.5 mL of solution.

Injection needles (stainless steel; 0.33 mm x 12 mm, 29 G x ½")

Pack size of 1 cartridge and 10 injection needles.

Ovaleap 450 IU/0.75 mL solution for injection

Cartridge (type I glass) with a rubber piston (bromobutyl rubber) and a crimp-cap (aluminium) with a septum (bromobutyl rubber), containing 0.75 mL of solution.

Injection needles (stainless steel; 0.33 mm x 12 mm, 29 G x ½")

Pack size of 1 cartridge and 10 injection needles.

Ovaleap 900 IU/1.5 mL solution for injection

Cartridge (type I glass) with a rubber piston (bromobutyl rubber) and a crimp-cap (aluminium) with a septum (bromobutyl rubber), containing 1.5 mL of solution.

Injection needles (stainless steel; 0.33 mm x 12 mm, 29 G x ½")

Pack size of 1 cartridge and 20 injection needles.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with

local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Human follicle stimulating hormone (FSH) is a glycoprotein (Molecular Weight is about 30,000 Da) and is characterised by two amino acid chains known as α and β. The β-chain confers biological activity. The α-chain is common to all gonadotrophins with specificity residing in the β-chain.

CAS number

146479-72-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine - Schedule 4

8. SPONSOR

Theramex Australia Pty Ltd

60 Margaret Street,

Sydney, NSW 2000

Phone: 1800 THERAMEX or 1800 843 726

9. DATE OF FIRST APPROVAL

10 March 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information