

NEW ZEALAND DATA SHEET

LUVERIS® 75 IU Powder for Injection

Lutropin alfa (rch)

NAME OF THE MEDICINE

LUVERIS contains lutropin alfa (rch).[#]

CAS-152923-57-4 (lutropin alfa); CAS-56832-30-5 (α -subunit); CAS-53664-53-2 (β -subunit).

Recombinant-hLH (r-hLH) is a human gonadotropin hormone, composed of two non-covalently linked non-identical subunits, designated α and β . The α -subunit is common to all four members of the gonadotropin hormone family. The α -subunit is formed by 92 amino acids and possesses two sites of N-linked glycosylation (Asn 52 and Asn 78). Five disulphide bonds contribute to its tertiary structure. The β -subunit, which is hormone specific, is 121 amino acids in length and possesses a single site of N-linked glycosylation (Asn 30). It contains six disulphide bridges.

[#] rch = Recombinant Chinese hamster

DESCRIPTION

Lutropin alfa is a recombinant human luteinising hormone (r-hLH). It is a glycoprotein hormone (Molecular Weight (MW) about 29,000 Da) that consists of two non-covalently linked, non-identical protein components designated as the α - and β -subunits. r-hLH is derived from a Chinese Hamster Ovary cell line that has been modified by the addition of human genes encoding the LH α - and β -chains.

The physicochemical, immunological and biological activities of r-hLH are comparable to those of human menopausal urinary-hLH (u-hLH). The main difference between u-hLH and r-hLH is that the u-hLH carbohydrate moieties are essentially capped with sulphate groups, while in r-hLH it is with sialic acid. Preclinical and clinical experience, however, indicate that this has no significant impact on the pharmacokinetic characteristics of these molecules.

LUVERIS is available as a sterile, lyophilised powder in vials containing lutropin alfa 75 IU. It is intended for co-administration with follitropin alfa as a subcutaneous injection after reconstitution with sterile Water for Injections. LUVERIS powder for injection also contains polysorbate 20, sodium phosphate - dibasic dihydrate, sodium phosphate - monobasic monohydrate, sucrose, methionine, phosphoric acid and sodium hydroxide to adjust the pH as excipients.

PHARMACOLOGY

Pharmacodynamics

Luteinising hormone binds on the ovarian theca (and granulosa) cells and testicular Leydig cells to a receptor shared with human chorionic gonadotrophin hormone (hCG). This LH/hCG transmembrane receptor is a member of the super-family of G protein-coupled receptors and has a large extracellular domain. The *in-vitro* binding affinities of r-hLH, pituitary hLH and hCG to the LH/hCG receptor on murine Leydig tumour cells are of similar orders of magnitude.

In the ovaries, during the follicular phase, LH stimulates the theca cells to secrete androgens, which will be used as the substrate by granulosa cell aromatase enzyme to produce oestradiol, supporting follicle stimulating hormone (FSH)-induced follicular development. At mid-cycle, high levels of LH trigger corpus luteum formation and ovulation. After ovulation, LH stimulates progesterone production in the corpus luteum by increasing the conversion of cholesterol to pregnenolone.

In the stimulation of follicular development in anovulatory women deficient in LH and FSH, the primary effect resulting from administration of LUVERIS is an increase in oestradiol secretion by the follicles, the growth of which is stimulated by r-FSH.

In clinical trials (studies 6253 and 21008), patients were defined by an endogenous serum LH level <1.2 IU/L as measured in a central laboratory. However, it should be taken into account that there are variations between LH measurements performed in different laboratories.

In these trials, achievement of an adequate follicular development as the optimal well-established and surrogate marker of conception was consistently found in 66.7% of patients with LH < 1.2 IU treated with FSH and 75 IU LUVERIS. This result was based on studies 6253 [66.7%] and 21008 [66.7%] and was calculated when risk of ovarian hyperstimulation syndrome (OHSS) and pregnancy outcome were considered as treatment successes. When risk of OHSS was considered as a treatment failure, adequate follicular development was found in 43.2% of patients (combined analysis of follicular development in studies 6253 and 21008).

Pharmacokinetics

The pharmacokinetics of lutropin alfa have been studied in pituitary desensitised female volunteers from 75 IU up to 40,000 IU.

The pharmacokinetic profile of lutropin alfa is similar to that of urinary-derived hLH. Following intravenous administration, lutropin alfa is rapidly distributed with an initial half-life of approximately one hour and eliminated from the body with a terminal half-life of about 10-12 hours. The steady state volume of distribution is around 10-14L. Lutropin alfa shows linear pharmacokinetics, as assessed by AUC, which is directly proportional to the dose administered. Total clearance is around 2 L/h, and less than 5% of the dose is excreted in the urine. The mean residence time is approximately 5 hours.

Following subcutaneous administration, the absolute bioavailability is approximately 60%; the terminal half-life is slightly prolonged. The lutropin alfa pharmacokinetics following

single and repeated administration of LUVERIS are comparable and the accumulation ratio of lutropin alfa minimal. There is no pharmacokinetic interaction with follitropin alfa when administered simultaneously.

CLINICAL TRIALS

The safety and efficacy of LUVERIS have been examined in five studies for induction of ovulation in women with hypogonadotropic hypogonadism (HH).

Pivotal studies

The safety and efficacy of LUVERIS administered subcutaneously and concomitantly with recombinant human FSH (r-hFSH) for ovulation induction in women with HH was assessed and confirmed in the following 2 international pivotal studies.

Study 6253

Study 6253 was a Phase II randomized, open-label, dose-finding study to determine the minimal effective dose and assess the safety of LUVERIS to support r-hFSH-induced follicular development in LH and FSH deficient anovulatory women. Patients were randomized to treatment with 0, 25, 75 or 225 IU LUVERIS concomitant with 150 IU of r-hFSH for up to 3 treatment cycles. Thirty-eight patients were enrolled and treated in a total of 53 treatment cycles.

The proportion of patients who fulfilled the primary efficacy endpoint criteria (at least one follicle ≥ 17 mm; $E_2 \geq 400$ pmol/L; mid-luteal phase $P_4 \geq 25$ nmol/L) was related to the dose of LUVERIS, both when excessive follicular development was not included as a success (0.0%, 14.3%, 44.4% and 50.0% for treatment with 0, 25, 75 and 225 IU LUVERIS, respectively; $p=0.0124$) and when excessive follicular development was included as a success (0.0%, 14.3%, 66.7% and 80.0% for treatment with 0, 25, 75 and 225 IU LUVERIS, respectively; $p=0.0001$).

Study 21008

The safety and efficacy of LUVERIS 75 IU administered subcutaneously or induction of ovulation in women with HH and severe gonadotrophin deficiency was assessed in this Phase III double-blind, placebo-controlled, randomized trial of 39 women.

The primary efficacy parameter in this single-cycle study was follicular development as defined by: (i) at least one follicle with a mean diameter of ≥ 17 mm, (ii) pre-ovulatory serum E_2 level ≥ 109 pg/mL (400 pmol/L) and (iii) mid-luteal phase P_4 level ≥ 7.9 ng/mL (25 nmol/L). Patients with excessive follicular development or who became pregnant were considered treatment successes from the perspective of the analysis.

The efficacy results for Study 21008 are summarized in Table 1a.

Table 1a Follicular Development Rate with *risk of OHSS* considered as a success (Population: ITT Patients)

Follicular Development	Placebo and r-hFSH (n=13) n (%)	75 IU r-hLH and r-hFSH (n=26) n (%)	Total (n=39) n (%)	p-value ^(a)
Yes	2 (15.4)	17 (65.4)	19 (48.7)	0.006
No	11 (84.6)	9 (34.6)	20 (51.3)	

(a) Fisher's Exact Test

The efficacy results for the same study are also assessed when risk of OHSS is considered as an efficacy failure in Table 1b.

Table 1b Follicular Development Rate and Ovulation with *risk of OHSS* considered as an efficacy failure (Population: ITT Patients)

Follicular Development	Placebo and r-hFSH (n=13) n (%)	75 IU r-hLH and r-hFSH (n=26) n (%)	Total (n=39) n (%)	p-value ^(a)
Yes	1 (7.7)	11 (42.3)	12 (20.8)	0.034
No	12 (92.3)	15 (57.7)	27 (69.2)	

(a) Fisher's Exact Test

Other Studies

The safety and efficacy of LUVERIS administered subcutaneously concomitantly with r-hFSH for ovulation induction in women with HH was also investigated in 3 additional studies.

Study 6905 was a Phase II/III open-label, randomized, multicenter study to determine the minimal effective dose and assess the safety of LUVERIS administered with r-hFSH to induce follicular development in anovulatory women with hypogonadotropic hypogonadism and moderate gonadotrophin deficiency. Forty patients were enrolled and treated.

Study 7798 was a Phase III multicenter study to assess the efficacy and safety of LUVERIS administered with r-hFSH for induction of follicular development in LH and FSH deficient anovulatory women and enrolled 15 patients.

Study 8297 was a Phase III multicenter, non-comparative study to assess the efficacy and safety of LUVERIS administered with r-hFSH for induction of follicular development in LH and FSH-deficient anovulatory women and enrolled 38 patients.

Among the 170 patients with HH enrolled in the 5 LUVERIS development studies, 154 were seeking fertility and of these 127 were treated with LUVERIS. Overall 41 of 127 (32%) LUVERIS treated patients (all doses) and 31 of 100 (31%) in the LUVERIS 75 IU dose group achieved a pregnancy over a total of 205 treatment cycles.

Table 2 Summary of pregnancies in cycles of women wishing to conceive

Treatment	Placebo or no LH				All r-hLH treated cycles					
	GF 6253	21008	GF 6905	Total no LH	GF 6253	GF 6905	21008	GF 8927	GF 7798	Total LH
Cycles	8	13	19	40	31	33	26	85	33	208
Cycles with hCG	2	3	15	20	17	30	13	64	28	152
Clinical pregnancies ¹	0	1	4	5	3	8	1	15	7	34
Miscarriages			1	1	1	1		1	2	5
Pregnancy loss after 20 weeks								1		1
Live birth simple			2	2	1	3		9	3	16
Live birth multiple		1 (twins with 1 NND ²)	1	2	1	3		4	2	10
Lost to follow up						1	1			

¹ Clinical pregnancy was defined by an ultrasound detection of a sac with or without heartbeat activity on day 35-42 after hCG administration

² NND = neonatal death

No direct comparison of r-hLH and r-hFSH versus human menopausal gonadotrophin (hMG) has been performed. Comparison with historical data suggests that the ovulation rate with the combination is similar to what can be obtained with hMG.

INDICATIONS

LUVERIS in association with a recombinant follicle stimulating hormone (FSH) 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 of less than 1.2 IU/L.

CONTRAINDICATIONS

LUVERIS is contraindicated in patients with:

- hypersensitivity to gonadotrophins or to any of the excipients
- ovarian, uterine or mammary carcinoma
- active, untreated tumours of the hypothalamus or pituitary gland
- ovarian enlargement or cyst of unknown aetiology
- gynaecological haemorrhages of unknown origin
- pregnancy and lactation

PRECAUTIONS

Before starting treatment, the couple's infertility should be assessed as appropriate and putative contraindications for pregnancy evaluated. It is recommended that LUVERIS is not used where an effective response is usually not expected, such as primary ovarian failure, malformation of the sexual organs or fibroid tumours of the uterus that are incompatible with pregnancy. In addition, patients should be evaluated for hypothyroidism, adrenocortical deficiency and hyperprolactinemia, and appropriate specific treatment given.

Ovarian Hyperstimulation Syndrome (OHSS)

A certain degree of ovarian enlargement is an expected effect of controlled ovarian stimulation. It is more commonly seen in women with polycystic ovarian syndrome and usually regresses without treatment.

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.

Mild to moderate OHSS is a common adverse effect of ovulation induction with gonadotrophins; the risk should be considered and discussed with women prior to treatment.

Independent risk factors for developing OHSS include young age, lean body mass, polycystic ovarian syndrome, higher doses of exogenous gonadotrophins, 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 Assisted Reproductive Technology (ART) cycles.

Adherence to recommended LUVERIS and FSH dosage and regimen of administration can minimise the risk of ovarian hyperstimulation. Monitoring of stimulation cycles by ultrasound scans, as well as oestradiol measurements, is recommended to identify risk factors early.

There is evidence to suggest that hCG plays a key role in triggering OHSS and that the syndrome may be more severe and more protracted if pregnancy occurs. Therefore, if monitoring results indicate a high risk of OHSS, or if signs of OHSS occur, it is recommended that hCG be withheld and the patient be advised to refrain from coitus or use barrier methods of contraception for at least 4 days. As OHSS may progress rapidly (within 24 hours) or over several days to become a serious medical event, patients should be followed for at least two weeks after hCG administration.

Mild manifestations of OHSS may include abdominal pain, abdominal discomfort and distension, or enlarged ovaries. Moderate OHSS may additionally present with nausea, vomiting, ultrasound evidence of ascites or marked ovarian enlargement. Severe OHSS further includes symptoms such as severe ovarian enlargement, weight gain, dyspnoea or oliguria. Clinical evaluation may reveal signs such as hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, pleural effusions, or acute pulmonary distress. Very rarely, severe OHSS may be complicated by ovarian torsion or thromboembolic events, such as pulmonary embolism, ischaemic stroke or myocardial infarction.

Mild or moderate OHSS usually resolves spontaneously. If severe OHSS occurs, it is recommended that gonadotrophin treatment be stopped, the patient be hospitalised and appropriate therapy be started.

Multiple Pregnancy

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 minimize the risk of twins of 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.

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 than following natural conception.

Thromboembolic Events

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 carry an increased risk of thromboembolic events.

Renal or Hepatic Impairment

Caution should be used and close monitoring considered when administering LUVERIS to patients with renal or hepatic impairment. There are currently no data available on the use of LUVERIS in patients with hepatic or renal impairment.

Porphyria

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

Congenital Anomalies

The prevalence of congenital anomalies after ART may be slightly higher than after spontaneous conceptions. Possible contributing factors include aspects inherent to 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.

Use in Pregnancy

Pregnancy Category B3

LUVERIS should not be administered during pregnancy as it may cause fetal harm when given to a pregnant woman (see CONTRAINDICATIONS). Data on a limited number of human pregnancies exposed inadvertently following controlled ovarian stimulation indicate no adverse reactions of gonadotrophins on pregnancy, embryonal or fetal development, parturition or postnatal development. In the case of inadvertent administration during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of LUVERIS.

Treatment of pregnant rats and rabbits with LUVERIS at doses of 10 IU/kg/day SC and above was associated with embryonic resorptions (approximately 0.4x and 0.8x clinical exposure at the maximum recommended clinical dose of 225 IU/day, based on body surface area, respectively). Teratogenicity was not observed in pregnant rats and rabbits dosed with LUVERIS at doses up to 20 IU/kg/day SC (approximately 0.8x and 1.6x clinical exposure, based on body surface area, respectively). Administration of 10 IU/kg/day LUVERIS to rats from late gestation to weaning resulted in adverse effects on the post-natal survival and growth of offspring.

Use in Lactation

LUVERIS should not be administered during lactation (see CONTRAINDICATIONS). Secretion of recombinant hLH (r-hLH) and/or its degradation products has been shown to occur in lactating rats.

Carcinogenicity

Long-term carcinogenicity studies have not been carried out.

Genotoxicity

Lutropin alfa was inactive in *in vitro* tests for gene mutation and chromosomal damage, and in an *in vivo* mouse micronucleus test.

Effects on the Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

INTERACTIONS WITH OTHER MEDICINES

LUVERIS should not be administered as a mixture with other medicines in the same injection, except follitropin alfa for which studies have shown that co-administration does not significantly alter the activity, stability, pharmacokinetic nor pharmacodynamic properties of the active substances.

ADVERSE EFFECTS

LUVERIS is used for the stimulation of follicular development in association with follitropin alfa. In this context, undesirable effects may be due to either or both of the substances used or their pharmacodynamic consequences.

There is considerable post-marketing safety experience with human luteinizing hormone (hLH) containing products of urinary origin. The safety profile of LUVERIS is expected to be very similar to that of urine derived hLH, with the exception of hypersensitivity reactions and application site disorders.

In clinical trials, a maximal score of all mild and moderate injection site reactions (bruising, pain, redness, itching or swelling) was reported in 12.7% (mild) and 2.7% (moderate) of the 2282 injections in 271 treatment cycles, respectively. Among the 170 patients treated, only 2 patients (1.2%) reported a severe injection site reaction.

OHSS was observed in 3.9% of treatment cycles with LUVERIS. Six serious OHSS reports (2.3%) occurred in 259 treatment cycles.

Ovarian cysts and enlargements are common. Complications including adnexal torsion and haemoperitoneum have been reported rarely with human menopausal gonadotrophin therapy.

Ectopic pregnancy may also occur, especially in women with a history of prior tubal disease.

The following definitions apply to the frequency terminology used hereafter:

Very Common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1,000$ to $< 1/100$
Rare	$\geq 1/10,000$ to $< 1/1,000$
Very Rare	$< 1/10,000$

General disorders and administration site condition

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

Nervous system disorders

Common: headache

Gastro-intestinal disorders

Common: nausea, vomiting, diarrhoea, abdominal pain, abdominal discomfort

Reproductive system and breast disorders

Common: mild or moderate OHSS (including symptomatology), ovarian cyst, breast pain, pelvic pain

Vascular disorders

Very rare: thromboembolism, usually associated with severe OHSS

Immune system disorders

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

The reported undesirable effects are in agreement with those reported for other hLH-containing products.

DOSAGE AND ADMINISTRATION

Treatment with LUVERIS should be initiated under the supervision of a physician experienced in the treatment of fertility problems. Self-administration of LUVERIS should only be performed by patients who are well-motivated, adequately trained and with access to expert advice.

In LH and FSH deficient women, the objective of LUVERIS therapy, in association with FSH is to develop a single mature Graafian follicle from which the oocyte will be liberated following administration of human chorionic gonadotrophin (hCG). LUVERIS should be given as a course of daily injections concomitantly with FSH. Since these patients are amenorrhoeic and have low endogenous oestrogen secretion, treatment can commence at any time. Nevertheless, the possibility of pregnancy should be first excluded by clinical or other means.

All clinical experience to date with LUVERIS in this indication has been gained with concomitant daily administration of follitropin alfa.

LUVERIS is intended for daily subcutaneous administration. The powder should be reconstituted, immediately prior to use, with the solvent provided. In order to avoid the injection of large volumes one vial of LUVERIS can be reconstituted together with one or two ampoules or vials of follitropin alfa 37.5 IU, 75 IU or 150 IU in 1 mL of solvent.

The majority of the women with very low LH levels (<1.2 IU/L as used in clinical studies, but this may vary from laboratory to laboratory) will have a poor ovarian response to recombinant human FSH (r-hFSH) alone. However, some women may have adequate follicular response. Clinicians will need to decide on a case by case basis whether to commence ovulation induction with r-hFSH alone or in combination with LUVERIS.

The efficacy studies have suggested that the minimum effective dose of LUVERIS is 37.5 IU. However, dose titration is recommended according to individual patient response.

Treatment should be tailored to the individual patient's response as assessed by measuring (i) follicle size by ultrasound and (ii) oestrogen response. A recommended regimen commences at 75 IU of lutropin alfa -daily with 75-150 IU FSH.

Clinical studies have employed doses of up to 225 IU of lutropin alfa and 150 IU follitropin alfa per day to induce follicular development. If a patient fails to respond after 3 weeks of treatment, the cycle should be abandoned and the patient should recommence treatment with a higher starting dose of follitropin alfa and/or LUVERIS than in the abandoned cycle.

If there is insufficient follicular growth, it is reasonable to increase the FSH dose, but if there is good follicular development with a low oestradiol level, this suggests that more LH may be required.

In clinical trials, LUVERIS has been associated with higher oestradiol levels than follitropin alfa alone. If an FSH dose increase is deemed appropriate, dose adaptation should preferably be at 7-14 day intervals and preferably with 37.5-75 IU increments.

When an optimal response is obtained, a single injection of 250 microgram of recombinant hCG (r-hCG) or 5,000 IU to 10,000 IU hCG should be administered 24-48 hours after the last LUVERIS and FSH injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination (IUI) may be performed. Luteal phase support should be considered since lack of endogenous gonadotrophins after ovulation may lead to premature failure of the corpus luteum.

If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at an FSH dosage lower than that of the previous cycle.

OVERDOSAGE

The effects of overdosage of LUVERIS are unknown, nevertheless there is a possibility that OHSS may occur which is further described in PRECAUTIONS.

Single doses of up to 40,000 IU of LUVERIS have been administered to healthy female volunteers without serious adverse events and were well tolerated.

Advise your patients to immediately contact their doctor or the Poisons Information Centre (in Australia telephone 131 126, in New Zealand telephone 0800 764 766) if they are concerned that they have given themselves too much LUVERIS.

PRESENTATION AND STORAGE CONDITIONS

LUVERIS is supplied in packs of 1, 3 or 10 vials. Each vial of LUVERIS contains 75 IU of lutropin alfa as lyophilised powder, and as excipients sucrose, sodium phosphate - dibasic dihydrate, methionine, sodium phosphate - monobasic monohydrate, polysorbate 20, phosphoric acid and sodium hydroxide for pH adjustment. Each pack also contains a corresponding number of vials containing 1 mL Water for Injections.

The lyophilised product must be stored below 25°C. Protect from light.
Shelf-life: 36 months

The reconstituted solution must be injected immediately as it contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

NAME AND ADDRESS OF THE SPONSOR

Supplied in New Zealand by:

Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks, Auckland

Supplied in Australia by:

Merck Serono Australia Pty Ltd
3-4/25 Frenchs Forest Road
Frenchs Forest NSW 2086

MEDICINE CLASSIFICATION

Prescription Medicine

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