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Lutropin Alfa

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Contents

Abstract

▲ Lutropin alfa is the first and only recombinant human form of luteinizing hormone (LH) developed for use in the stimulation of follicular development.

▲ Dose-finding studies revealed a significant dose-dependent increase in the rate of optimal follicular development among women with hypogonadotropic hypogonadism and profound LH deficiency (<1.2 IU/L) who received subcutaneous lutropin alfa 0–225 IU/day plus follitropin alfa.

▲ Similarly, in a double-blind, randomized study, the rate of optimal follicular development was significantly higher in women with hypogonadotropic hypogonadism and profound LH deficiency receiving subcutaneous lutropin alfa 75 IU/day plus follitropin alfa than in those receiving placebo plus follitropin alfa.

▲ Lutropin alfa with follitropin alfa may also be of benefit in certain subgroups of normogonadotropic women (e.g. those with an inadequate response to prior follitropin alfa monotherapy, those aged ≥35 years, and those with profound LH downregulation or who required excessive exogenous follitropin alfa). However, one study in older women (≥35 years) did not show any advantage of lutropin alfa supplementation.

▲ Once-daily subcutaneous lutropin alfa was generally well tolerated in hypogonadotropic hypogonadal women, with the majority of adverse events being of mild to moderate severity.

Features and properties of lutropin alfa (Luveris®)	
Featured indication	
Stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound luteinizing hormone (LH) deficiency (<1.2 IU/L) [US], or in women with severe LH and follicle-stimulating hormone deficiency (EU). In clinical trials, these patients were defined by an endogenous serum LH level <1.2 IU/L	
Mechanism of action	
Stimulates theca cells to secrete androgens, which are used as substrate by granulosa cell aromatase enzyme to produce estradiol	
Dosage and administration	
Dose	75 IU
Frequency of administration	Once daily
Route of administration	Subcutaneous
Pharmacokinetic profile (single dose of subcutaneous lutropin alfa 150 IU; mean values unless otherwise stated)	
Peak serum drug concentration	1.1 IU/L
Median time to maximum serum drug concentration	6 h
Area under the serum drug concentration-time curve	44 IU • h/L
Terminal elimination half-life	≈14 h
Bioavailability (10 000 IU)	56%
Adverse events (incidence ≥5%)	
Headache, nausea, ovarian hyperstimulation, breast pain, abdominal pain, ovarian cyst	

The single most common cause of infertility in females is anovulation, with ≥40% of infertile women having an ovulatory problem.[1] Exogenous gonadotropins in combination with gonadotropin releasing hormone (GnRH) agonists have been used to induce follicular stimulation in these patients.[2,3]

Ovulatory disorders are classified into seven groups by the WHO, based on the levels of endogenous prolactin, gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) and estrogens.[1] Hypogonadotropic hypogonadism (WHO group I anovulation) is a rare condition, characterized by reduced hypothalamic or pituitary activity resulting in abnormally low serum levels of FSH and LH, and negligible estrogen activity.[1,4,5] These women are amenorrhoeic, have no evidence of endogenous estrogen production, have non-elevated prolactin levels, normal or low FSH levels and no detectable space-occupying lesion.[1,4,5] Pulsatile GnRH therapy is an option in hypogonadotropic hypogonadal women with intact pituitary function as it restores the periodic release of both FSH and LH;[6,7] GnRH agonists with pulsatile GnRH therapy have also been used.[6] However, in patients with pituitary disease, and those who do not respond adequately to treatment, daily injections of gonadotropins are an alternative.[4,5,7] Human menopausal gonadotropin (hMG) [a urinary extract containing FSH and LH] used to be the only exogenous source of LH.[8,9] GnRH agonists and hMG are not approved for use in hypogonadotropic hypogonadal women but are used off-label. Additionally, the use of hMG for ovarian stimulation has several limitations, including an inherent variability in LH content of the hMG preparation, making it difficult to control the LH dose being administered.[8-10]

Both FSH and LH activity are needed for optimal follicular growth and maturation, and although FSH and LH act individually, they complement each other in regulating follicular growth and maturation (reviewed by Filicori and Cognigni[11]). The role of LH in ovarian stimulation has been reviewed extensively by Alviggi et al.[12,13] Lutropin alfa (Luveris®)[1] is the first and only recombinant human form of LH.[14] Synthesis of lutropin alfa in genetically modified Chinese hamster ovary cells, using recombinant DNA technology,[15] ensures a high-quality product, free of urinary impurities, and with the same isoform profile.[9] Consistent hormone content and quality between batches of lutropin alfa provides the possibility of precise control of LH activity in patients who require LH therapy.[9,16]

Lutropin alfa has been approved in numerous countries worldwide, for subcutaneous administration in combination with recombinant FSH (follitropin alfa, GONAL-f®), to stimulate follicular development in certain infertile women. In the EU, a combination of lutropin alfa 75 IU and follitropin alfa 150 IU (Pergoveris™), for subcutaneous administration, is also approved for the stimulation of follicular development in women with severe LH and FSH deficiency.[17] This article focuses on the use of subcutaneous lutropin alfa in women undergoing fertility treatment.

1. Pharmacodynamic Profile

LH belongs to a family of heterodimeric glycoprotein hormones including FSH, human chorionic gonadotropin (hCG) and thyroid stimulating hormone, each with a unique β-subunit that confers physiological specificity.[9] LH binds rapidly and reversibly to a receptor that also binds hCG and is expressed on the granulosa and theca cells.[9] In the ovaries, during the follicular phase, LH stimulates the theca cells to produce androgens, which are converted by the granulosa cell aromatase enzyme to estradiol (E_2), which, in turn, supports FSH-induced follicular development.[11,18] At mid-cycle, ovulation and corpus luteum formation are triggered by high levels of LH, followed by progesterone production in the corpus luteum.[18] Furthermore, during later stages of follicle development, granulosa cells also express LH receptors and become receptive to LH stimulation (reviewed by Filicori et. al.[19]). Consequently, LH can influence both the theca and granulosa cells, and exert virtually all the physiological actions of FSH.[19]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Lutropin alfa is a glycoprotein composed of non-covalently bound α- and β-subunits, and has activity similar to that of native LH.[9,15] In terms of stimulating follicular development in anovulatory women who are deficient in LH and FSH, the primary effect of lutropin alfa is to increase the secretion of estradiol by the follicles.[18]

- Once-daily subcutaneous lutropin alfa supported follitropin alfa-induced follicular development, according to the results of trials in women with hypogonadotropic hypogonadism.[4,5,15,20-22] Results of these studies are discussed further in section 3.

- Administration of high-dose lutropin alfa alone during late follicular maturation triggered follicular growth arrest and prevented follicles from reaching the late antral stage in hypogonadotropic hypogonadal women (n = 20; mean age ≈31 years) in a randomized, double-blind, placebo-controlled study.[23] Patients were randomized to these treatment groups once at least one follicle was 10–13 mm in diameter. The mean number of follicles of ≥11 mm in diameter was significantly ($p < 0.05$) lower in women receiving lutropin alfa 225 IU once daily plus placebo (1.5) than in those receiving subcutaneous follitropin alfa 112.5–262.5 IU once daily plus placebo (4.2) or lutropin alfa plus follitropin alfa (6.0). These results suggest that lutropin alfa has a 'ceiling effect', whereby follicles exposed to inappropriately high concentrations of the hormone enter atresia or become prematurely luteinized, resulting in compromised oocyte development.[23]

- In women with infertility due to anovulation (WHO group II) and over-responding to follitropin alfa during ovulation induction, lutropin alfa administered along with follitropin alfa during late follicular phase may promote the growth of a dominant follicle and cause atresia of secondary follicles.[24] In a randomized, placebo-controlled study (n = 153), the proportion of patients with only one follicle ≥16 mm in diameter was 20.7–32.1% in lutropin alfa 150–1325 IU plus follitropin alfa 37.5 IU recipients compared with 13.3% in placebo plus follitropin alfa recipients. Significantly more lutropin alfa 660 IU plus follitropin alfa than placebo plus follitropin alfa recipients had one follicle ≥16 mm in diameter (32.1% vs 13.3%; $p = 0.048$). These results support the hypothesis that lutropin alfa has a 'ceiling effect' on follicular development.[24]

- In women (n = 42) with insufficient ovarian response to ovarian stimulation (who had undergone previous stimulation with >3000 IU of recombinant FSH), lutropin alfa administered along with follitropin alfa during the late follicular phase may improve oocyte quality by reducing apoptosis in cumulus cells that are involved in the control of oocyte maturation.[25] In a prospective, randomized study, there were significantly fewer ($p < 0.01$) immature oocytes in women receiving lutropin alfa 75–150 IU/day plus follitropin alfa 225 IU/day than in those receiving follitropin alfa alone (0.58 vs 2.33). Lutropin alfa plus follitropin alfa recipients had higher ($p < 0.01$) pregnancy (45% vs 25%) and implantation (16% vs 13%) rates relative to follitropin alfa alone recipients.[25]

- Lutropin alfa 150 IU/day administered in association with GnRH antagonists (flexible dose), compared with a standard GnRH agonist short protocol, may improve oocyte quality and the maturation process, resulting in an increase in the number of mature oocytes.[26] In 133 patients undergoing *in vitro* fertilization, patients receiving GnRH antagonist treatment in association with lutropin alfa had more mature oocytes than those undergoing the GnRH antagonist short protocol (7 vs 5; $p < 0.05$).[26]

2. Pharmacokinetic Profile

The pharmacokinetic profile of lutropin alfa is similar to that of urinary-derived human LH.[27] As the concentration of lutropin alfa following a 75 IU dose is too small to allow proper quantification of its pharmacokinetic parameters, this section focuses on the 150 IU subcutaneous dose of the agent; however, where data are limited other routes of administration and supplemental data from the US prescribing information[15] are also discussed. Pharmacokinetics of lutropin alfa were assessed in three randomized, crossover studies.[27-29] Healthy, pituitary-downregulated women (12 in each study) received single intravenous doses of lutropin alfa 300, 10 000 and

40 000 IU,[27] single intravenous, intramuscular and subcutaneous doses of lutropin alfa 10 000 IU,[29] or single doses of subcutaneous lutropin alfa 150 IU and subcutaneous follitropin alfa 150 IU administered alone and together, followed by subcutaneous lutropin alfa 150 IU/day plus follitropin alfa 150 IU/day administered for 7 days.[28]

- Following administration of a single subcutaneous dose of lutropin alfa 150 IU, a mean peak serum drug concentration (C_{max}) of 1.1 IU/L was reached after a median of 6 hours (t_{max}).[28] The mean area under the serum drug concentration-time curve (AUC) from time zero to infinity (AUC_∞) was 44 IU • h/L and the mean absorption half-life was 1.9 hours.[28] Lutropin alfa pharmacokinetics were adequately described by a one-compartment model with first-order absorption.[28] The mean absolute bioavailability of lutropin alfa was 56% following a single subcutaneous dose of 10 000 IU.[29]
- With repeat administration of subcutaneous lutropin alfa 150 IU/day (in combination with follitropin alfa), steady state was almost reached by day 2.[28] Modest accumulation was seen with repeat administration, with an accumulation ratio of 1.6. The mean AUC from time 0 to 24 hours, the mean C_{max} and the median t_{max} values at day 1 were 15 IU • h/L, 1.1 IU/L and 6 hours, respectively, whereas at day 7, the corresponding values were 22 IU • h/L, 1.3 IU/L and 5 hours.[28]
- Following administration of single doses of intravenous lutropin alfa 300–40 000 IU, the estimated mean volume of distribution at steady state was 8–10 L, with a mean residence time of 5–6 hours.[27]
- Subcutaneous lutropin alfa 150 IU was eliminated from the body with a mean terminal elimination half-life of ≈14 hours, and <5% was excreted unchanged in the urine.[28] Following administration of intravenous lutropin alfa 10 000 IU, the systemic serum clearance was ≈2.5 L/h.[29]
- Concomitant follitropin alfa does not affect the pharmacokinetics of lutropin alfa, and vice versa.[28] C_{max}, t_{max} and AUC_∞ values for lutropin alfa and follitropin alfa were similar following administration of single-dose subcutaneous lutropin alfa 150 IU and follitropin alfa 150 IU alone or combined.[28] Other drug interaction studies with lutropin alfa have not been conducted.[15]
- Pharmacokinetic parameters of lutropin alfa in the elderly or paediatric population, and in patients with renal or hepatic impairment have not been established.[15]

3. Therapeutic Efficacy

Hypogonadotropic Hypogonadal Women

The efficacy of subcutaneous lutropin alfa in promoting follicular development in hypogonadotropic hypogonadal women (18–40 years of age) has been evaluated in two randomized, multicentre, dose-finding studies,[5,20] in a randomized, double-blind, placebo-controlled, multicentre study[21] and its open-label extension,[22] and in a noncomparative, multicentre trial.[4] Two of the trials are available only as abstracts,[20,21] while additional data for two studies[5,21] have been reported in the US prescribing information.[15] Trial sizes are small because of the rarity of the condition (n = 38–40).

Entry criteria for gonadotropin levels differed slightly between the two dose-finding studies.[5,20] Patients had LH and FSH levels of <1.2 IU/L and <5.0 IU/L in one study,[5] and ≤13.3 IU/L and ≤10.85 IU/L in the other.[20] Patients included in one study were required to have a negative progesterone (P_4) challenge test and to have ultrasound-detected ≤10 (using vaginal probe) or ≤13 (abdominal probe) small follicles (≤10 mm) [one patient in this study had a baseline serum LH level of 1.3 IU/L].[5] In the double-blind trial, serum LH, FSH and E_2 levels were <1.2 IU/L, <5 IU/L and <600 pg/mL, respectively,[21] and in the noncomparative study, mean LH and FSH levels were 1.3 and 2.8 IU/L at baseline.[4] Exclusion criteria included a previous history of severe ovarian hyperstimulation syndrome (OHSS),[4,5] treatment with pulsatile GnRH, gonadotropins or estrogen-progesterone replacement therapy within 1 month prior to screening[5] and ultrasound evidence of polycystic ovarian disease.[4,20] In comparative trials, treatment groups were generally well matched in terms of baseline hormonal levels.[4,20]

Patients received once-daily subcutaneous lutropin alfa 0, 25, 75 or 225 IU coadministered with follitropin alfa 150 IU/day (for up to 20 days[5]) in the two dose-finding studies.[5,20] Follicular growth was monitored by ultrasound and serum E_2 measurements, and ovulation was induced after the last day of lutropin alfa plus follitropin alfa administration with a single intramuscular injection of hCG 10 000 IU.[5] Each patient received at least one cycle (cycle A; n = 38) of therapy, although in some women therapy was continued for one (cycle B; n = 9) or two (cycle C; n = 5) additional cycles. The lutropin alfa dosage in cycles B and C was determined by patient response (follicular development) during previous cycles, while the dosage of follitropin alfa was maintained at 150 IU/day.[5]

In the double-blind trial, patients received lutropin alfa 75 IU/day plus follitropin alfa 150 IU/day or placebo plus follitropin alfa 150 IU/day.[21] In the extension of this trial,[21] 31 of 39 patients, who had received lutropin alfa plus follitropin alfa (n = 20) or placebo plus follitropin alfa (n = 11) during the lead-in trial, were treated with lutropin alfa 75 IU/day and follitropin alfa 75–225 IU/day over multiple cycles.

In the noncomparative study, patients were treated with once-daily follitropin alfa 150 IU from days 1–5.[4] From day 6 onwards, follitropin alfa was administered according to the ovarian response in combination with a fixed dosage of once-daily lutropin alfa 75 IU. Follicular growth was monitored by ultrasound and serum estradiol measurements, and ovulation was induced after the last day of lutropin alfa plus follitropin alfa administration with a single subcutaneous injection of hCG 10 000 IU. Each patient received at least one cycle (cycle A; n = 38) of therapy, although in some women, therapy was continued for one (cycle B; n = 29) or two (cycle C; n = 17) additional cycles. The dosage of lutropin alfa in cycles B and C was determined by patient response (follicular development) during previous cycles, while the dosage of follitropin alfa was maintained at 150 IU/day, or reduced to a starting dosage of 75 IU/day if there had been a hyper-response in previous cycles.[4]

During treatment, five patients (cycle A) in one study[5] and four patients (all cycles) in another study[4] did not receive hCG due to the risk of OHSS.

The primary efficacy endpoint was the proportion of patients with optimal follicular development defined as at least one follicle with a mean diameter of ≥17[5,15,20-22] or ≥18[4] mm, plus a midluteal P_4 level ≥25–30 nmol/L,[5,15,20-22] with a preovulatory serum E_2 level ≥400[5,15,21,22] or ≈600[20] pmol/L.

Effect on Follicular Development

- Use of lutropin alfa in combination with follitropin alfa induced follicular growth in hypogonadotrophic hypogonadal women.[4,5,15,20,21] In one dose-finding trial, a significant dose-dependent increase in the rate of optimal follicular development was seen during cycle A in women (n = 34 evaluable) receiving lutropin alfa 0–225 IU/day plus follitropin alfa, regardless of whether excessive follicular development was (p = 0.0001) or was not (p = 0.0124) included as success (figure 1a).[5] Although no statistical analysis was conducted, the proportion of patients with optimal follicular development over all three cycles also appeared to increase with lutropin alfa dosage (figure 1a).
- In the intent-to-treat patient population (n = 38) of this study,[5] a significant (p = 0.028) dose-dependent increase in the rate of optimal follicular development was seen in women receiving lutropin alfa 0–225 IU/day plus follitropin alfa when excessive follicular development was included as success, but not when it was considered as failure.[15]
- A lutropin alfa dosage of 75 IU/day was sufficient for promoting optimal follicular development and steroidogenesis in 46% of treatment cycles.[5]
- Lutropin alfa had a dose-dependent effect on serum E_2 levels; on the last day of follitropin alfa administration, serum E_2 levels were 65, 195, 1392 and 2441 pmol/L in recipients of lutropin alfa 0, 25, 75 and 225 IU/day, respectively.[5] In the treatment groups, corresponding endometrial thickness on the last day of treatment was 3.5, 3.2, 7.6 and 7.8 mm (values estimated from a graph), and androstenedione levels on the day of hCG administration were 1.0, 3.2, 7.8 and 6.7 nmol/L.[5]

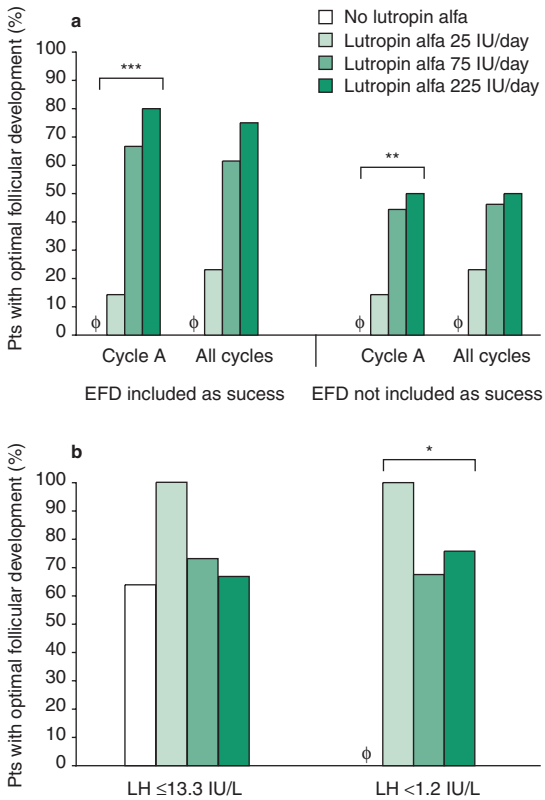

Fig. 1. Efficacy of lutropin alfa in stimulating follicular development in hypogonadotropic hypogonadal women.[5,20] Rate of optimal follicular development (**a**) stratified according to cycles of therapy[5] or (**b**) luteinizing hormone (LH) levels[20] in two randomized, multicentre dose-finding studies in women aged 18–40 years (n = 38[5] and 40[20] evaluable). Patients (pts) were treated with lutropin alfa 0–225 IU/day coadministered with follitropin alfa 150 IU/day[5,20] for up to 20 days.[5] Φ indicates zero; **EFD** = excessive follicular development; * p = 0.039, ** p = 0.0124, *** p = 0.0001 for a dose-response relationship.

• In the second dose-finding study,[20] the rate of follicular development was similar among recipients of lutropin alfa 0–225 IU/day (figure 1b). However, when the analysis was restricted to patients with profound LH deficiency at baseline (i.e. LH <1.2 IU/L; similar to the entry criteria in the other dose-finding study[5]), a significant (p = 0.039) dose-response relationship was seen (figure 1b).[20]

• In the double-blind trial, women receiving lutropin alfa 75 IU/day plus follitropin alfa showed significantly higher rates of optimal follicular development than the recipients of placebo plus follitropin alfa, regardless of whether excessive follicular development was (p = 0.006)[15,21] or was not (p = 0.034)[15] included as success (figure 2).

• Rates of ovulation (defined by mid-luteal phase serum P_4 levels ≥25 nmol/L) were 46% with lutropin alfa plus follitropin alfa versus 15% with placebo plus follitropin alfa, mean preovulatory serum E_2 levels were 549 versus 78 pg/mL, and mean endometrial thickness was 7.4 versus 5.0 mm (statistical analysis not reported).[15]

• In the extension of the double-blind trial, high rates of follicular development were observed in lutropin alfa plus follitropin alfa recipients. Follicular development was observed in 87.1% of all patients receiving lutropin alfa and follitropin alfa over three cycles of treatment.[22] In patients receiving follitropin alfa plus placebo during the lead-in trial followed by lutropin alfa plus follitropin alfa during the extension phase, 63.6% showed follicular development; 9.1% (one patient) of follitropin alfa plus placebo recipients had achieved follicular development during the initial double-blind phase.[22]

• A high rate of optimal follicular development in patients receiving lutropin alfa plus follitropin alfa was also seen in a noncomparative trial.[4] A lutropin alfa dosage of 75 IU/day was effective in 94% of treatment cycles.[4]

Pregnancy Rates

• In the extension trial, after three cycles of treatment, pregnancy (positive pregnancy test) was achieved in 64.5% and clinical pregnancy in 51.6% of all patients receiving lutropin alfa plus follitropin alfa (n = 31).[22] In patients who had received placebo plus follitropin alfa during the double-blind lead-in trial, clinical pregnancies in the extension phase occurred in 36.4% of patients after treatment with one cycle of lutropin alfa plus follitropin alfa.[22]

• In the noncomparative trial, the pregnancy rate per cycle with hCG administration was 22.4%. Over the three cycles, pregnancy was achieved in 15 of 38 (39.5%) patients.[4]

• Several case reports of women (aged 28–34 years) with Kallman's syndrome, characterized by primary amenorrhoea, anosmia and hypogonadotropic hypogonadism, reported preg-

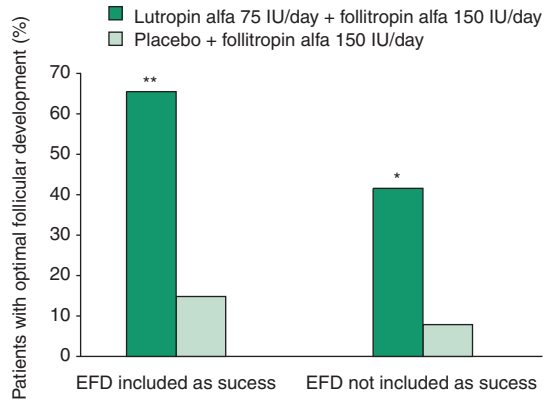

Fig. 2. Efficacy of lutropin alfa in hypogonadotropic hypogonadal women.[15,21] Rate of optimal follicular development after cycle 1 of therapy in a randomized, double-blind, placebo-controlled, multicentre trial in women receiving lutropin alfa 75 IU/day (n = 26) or placebo (n = 13), coadministered with follitropin alfa 150 IU/day.[15,21] **EFD** = excessive follicular development. * p = 0.034, ** p = 0.006 vs placebo.

nancies after lutropin alfa therapy.[30-32] Patients received lutropin alfa in combination with follitropin alfa for ovulation induction,[30-32] and also for follicular maturation.[32]

Normogonadotropic Women Undergoing Fertility Treatment

Apart from one study that showed benefit with lutropin alfa plus follitropin alfa in terms of implantation and clinical pregnancy rates in an unselected group of women,[33] results from studies in normogonadotropic women[34-43] and in those who are defined as poor responders to ovarian stimulation for *in vitro* fertilization (patients aged ≥40 years with elevated 3-day FSH levels [≥10 mIU/mL])[44] have shown that the addition of lutropin alfa to purified FSH[34] or follitropin alfa[35-44] is generally not associated with clinical advantages in the overall population. Similarly, a Cochrane review of randomized clinical trials showed that there was no significant difference in terms of live births (primary outcome) between GnRH downregulated women receiving lutropin alfa plus follitropin alfa and those receiving follitropin alfa alone, although, there was some benefit of combination therapy in women who were poor responders to ovarian stimulation.[45]

However, there do appear to be subgroups of normogonadotropic women who benefit from lutropin alfa therapy. This section focuses on the results from studies in women with inadequate response to prior follitropin alfa monotherapy (n = 117[46] and 126[47]), in older women aged ≥35 years (n = 39–120)[37,38,48] and in women with profound LH downregulation (n = 22) or who required excessive exogenous follitropin alfa (n = 8);[49] three of the studies were subgroup analyses.[37,38,49] Results were obtained from randomized studies conducted in normogonadotropic women (aged 18–40 years) with infertility due to various reasons who were undergoing assisted reproduction.[37,38,46-49] One trial was nonblind,[38] one was non-assessor-blind[37] and one was investigator-blind (i.e. biologists and clinicians performing oocyte collection);[46] two trials[38,46] were of multicentre design. Blinding was not reported in two trials.[47,49]

Other inclusion criteria included having normal ovulatory cycles,[37,38,46-49] basal FSH levels of ≤9–12 IU/L[37,38,46,48] and having no more than two previous assisted reproduction attempts.[38,46] Patients included in one study had serum E_2 levels <180 pg/mL and no follicles with a mean diameter >10 mm on day 8 after stimulation with follitropin alfa.[46] In another study, women were undergoing their first cycle of assisted reproduction.[48] Exclusion criteria included any known endocrinopathy/illness[49] or clinically significant systemic disease,[38] serum/plasma LH : FSH ratio >2[38] or the presence of polycystic ovarian disease or only one ovary.[46]

Following pituitary desensitization using GnRH agonists (buserelin,[37] leuprorelin[38] or triptorelin[46,48,49]), ovarian stimulation was induced with subcutaneous follitropin alfa.[37,38,46-49] On days 5–10 of stimulation, patients were randomized to continue receiving follitropin alfa alone,[37,38,46-49] to receive follitropin alfa plus lutropin alfa,[37,38,46-49] or hMG.[47] Where specified, the initial dosage of follitropin alfa was 150–450 IU/day (adjusted as needed)[37,38,46-49] and the lutropin alfa dosage was 75–150 IU/day,[47] or fixed at 75[37,49] or

150[38,46,48] IU/day. Intramuscular (7500[47] or 10 000 IU[37,38,46,49]) or subcutaneous (250 μg[48]) hCG was subsequently administered to induce final maturation.

Where specified, primary endpoints included the number of metaphase II oocytes retrieved,[38,48] the number of cumulus-oocyte complexes retrieved,[46] ovarian stimulation characteristics (including duration of ovarian stimulation and total dose of follitropin alfa),[48] implantation rate,[47,48] the pregnancy rate per embryo transfer,[47] clinical pregnancies[48] and the live birth rate per started cycles.[47]

Earlier, a preliminary study in women with an inadequate response to follitropin alfa had shown that lutropin alfa 150 IU/day was better than 75 IU/day when administered concomitantly with follitropin alfa 150–300 IU in terms of the mean number of oocytes retrieved.[50] Thus, this was the dosage subsequently used in the trials that followed.

- Adding lutropin alfa 150 IU/day to follitropin alfa was more effective than increasing the follitropin alfa dosage or using hMG in women with an inadequate response to follitropin alfa alone.[46,47] In one study, the mean number of cumulus-oocyte complexes retrieved (9.0 vs 6.1; $p < 0.01$) and the mean number of mature oocytes (7.8 vs 4.7; $p < 0.01$) were significantly higher in recipients of lutropin alfa plus follitropin alfa than in patients receiving follitropin alfa alone.[46]

- There were no significant between-group differences in the cumulative implantation rate (14.2% with lutropin alfa plus follitropin alfa vs 10.5% with follitropin alfa alone), the cumulative pregnancy rate (37.2% vs 29.3%), the cumulative abortion rate (17.0% vs 22.0%) and the cumulative ongoing pregnancy rate (32.5% vs 22.0%).[46]

- In another study, lutropin alfa plus follitropin alfa recipients had significantly higher pregnancy (54% vs 24.4% and 11.0%; $p < 0.05$) and implantation rates (36.8% vs 14.1% and 7.4%; p value not stated) than patients receiving a higher dosage of follitropin alfa or those receiving hMG.[47] In addition, the live birth rate was 40.7% in lutropin alfa plus follitropin alfa recipients, 22.0% in patients receiving follitropin alfa alone and 18.0% in those receiving hMG.[47]

- The addition of lutropin alfa to follitropin alfa in women aged ≥35 years did not show any advantage in terms of ovarian stimulation characteristics, number of oocytes retrieved, implantation rates or clinical pregnancies in one study.[48] There were no significant between-group differences in the duration of ovarian stimulation (10.1 days with lutropin alfa plus follitropin alfa vs 11.4 days with follitropin alfa alone), total dose of follitropin alfa (2330 vs 2620 IU), implantation rates (20.6% vs 21.7%) and clinical pregnancies (24 vs 25). Moreover, the mean number of oocytes retrieved (7.9 vs 6.3), the mean number of metaphase oocytes (6.9 vs 5.5), as well as the number of oocytes fertilized (5.0 vs 4.0) were significantly (all $p < 0.01$) higher in recipients of follitropin alfa than in those receiving lutropin alfa plus follitropin alfa.[48]

- However, subgroup analyses in two other studies showed that supplemental lutropin alfa might be beneficial in these women.[37,38] In one study, the implantation rate was significantly higher in women aged ≥35 years who received lutropin alfa plus follitropin alfa than in those receiving follitropin alfa alone (36.4% vs 13.3%; $p < 0.05$).[37] In addition, the total dose of follitropin alfa was significantly lower with combination therapy than with follitropin alfa alone (2225 vs 2797 IU; $p < 0.05$).[37]

- In another study, the mean number of metaphase II oocytes retrieved in women aged ≥35 years was 9.3 in those receiving lutropin alfa 150 IU/day plus follitropin alfa and 8.3 in those receiving follitropin alfa alone.[38] There were no significant between-group differences in implantation rates (21.7% vs 15.7%); however, in women aged ≥35 years who were undergoing their first assisted reproduction cycle, pregnancy rate was significantly higher with lutropin alfa plus follitropin alfa than with follitropin alfa alone (45.8% vs 22.5%; $p = 0.027$).[38]

- Supplementation with lutropin alfa 75 IU/day also appeared beneficial in women with profound downregulation of LH (i.e. serum LH level <1.0 IU/L) or who required excessive follitropin alfa (>2500 IU).[49] Implantation rates were significantly

higher in lutropin alfa plus follitropin alfa recipients than in recipients of follitropin alfa alone both in patients with profound LH downregulation (15.4% vs 0%; $p < 0.05$) and in those requiring excessive follitropin alfa (71.4% vs 7.1%; $p < 0.001$).[49]

- Additionally, in the Cochrane review,[45] a pooled analysis of data from three trials[44,46,47] involving women who were poor responders to ovarian stimulation showed that the estimate of ongoing pregnancy per woman was significantly higher in patients receiving lutropin alfa plus follitropin alfa than in those receiving follitropin alfa alone (odds ratio 1.85 [95% CI 1.1, 3.1]).

4. Tolerability

Tolerability data concerning subcutaneous lutropin alfa were obtained from the studies in hypogonadotropic hypogonadal women[4,5,20] (study design details discussed in section 3) and a pooled analysis of six clinical trials reported in the US prescribing information.[15] Data in this section focus on the recommended lutropin alfa dosage of 75 IU/day.

- Lutropin alfa was generally well tolerated in hypogonadotropic hypogonadal women undergoing fertility treatment,[4,20] with no relationship seen between the lutropin alfa dosage and the adverse event rate.[20] The majority of adverse events were of mild to moderate severity;[4,20] no serious adverse events were reported.[20]
- Adverse events were reported in 42.4% of women receiving lutropin alfa 75 IU/day plus follitropin alfa (dosage not reported) and in 46.5% of patients receiving follitropin alfa alone, according to the results of the pooled analysis.[15] The most commonly reported treatment-emergent adverse events in lutropin alfa recipients included headache, nausea, ovarian hyperstimulation, breast pain, abdominal pain and ovarian cyst (figure 3).
- Over 90% of injections were associated with no local reactions[4,5] or local reactions of only mild severity;[5] no symptoms suggestive of immune reaction were reported.[5] Lutropin alfa administration was not associated with significant changes in laboratory parameters.[4,5]

5. Dosage and Administration

Subcutaneous lutropin alfa 75 IU once daily should be administered in combination with follitropin alfa 75–150 IU/day, as two separate injections, in the initial treatment cycle.[15,18] Therapy should be monitored by ovary ultrasonography and serum E_2 levels, and the duration of treatment should usually not exceed 14 days, unless signs of

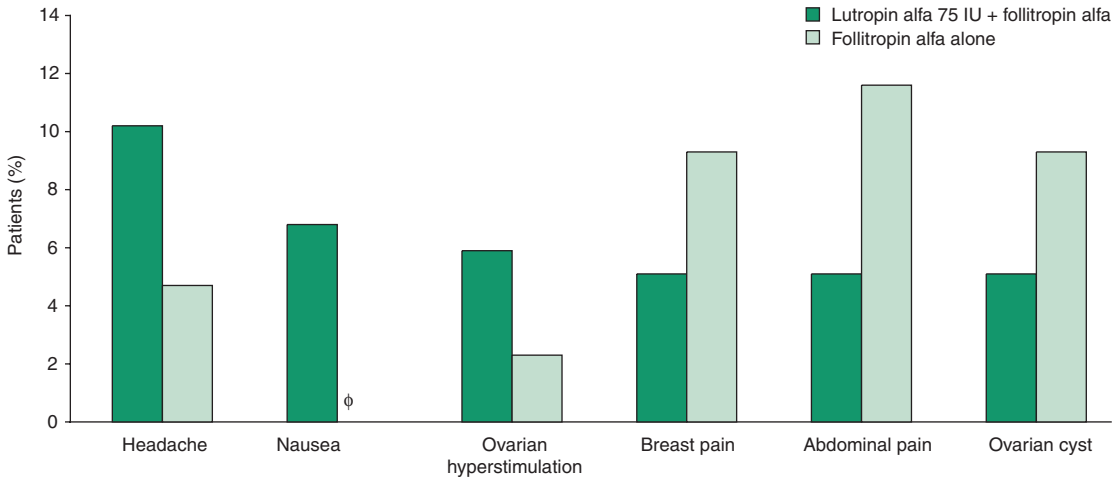

Fig. 3. Tolerability profile of lutropin alfa. Incidence (occurring in ≥5% of lutropin alfa recipients) of treatment-emergent adverse events in infertile hypogonadotropic hypogonadal women receiving subcutaneous lutropin alfa 75 IU/day plus follitropin alfa (dosage not reported) [n = 118] or follitropin alfa alone (n = 43), in a pooled analysis of six clinical studies.[15] Φ indicates zero.

imminent follicular development are present.[15,18] hCG should be administered 24–48 hours after the last dose of lutropin alfa and follitropin alfa to complete follicular development and effect ovulation in the absence of an endogenous LH surge.[15,18] Drug dosages in subsequent cycles should be individualized on the basis of response in the preceding cycle.[15,18]

In addition, a combination of lutropin alfa 75 IU and follitropin alfa 150 IU for subcutaneous administration is also available in the EU, which is administered as a daily injection.[17]

Local manufacturer's prescribing information should be consulted for comprehensive dosage and administration guidelines, contraindications and other precautions.

6. Lutropin Alfa: Current Status

Subcutaneous lutropin alfa, the first and only recombinant human form of LH, in conjunction with follitropin alfa, has been approved in numerous countries worldwide. In the US, it is approved for the stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (<1.2 IU/L).[14,15] In the EU, its use for stimulating follicular development is approved in women with severe LH and FSH deficiency.[18] In addition, in the EU, a combination of lutropin alfa 75 IU and follitropin alfa 150 IU (Pergoveris™) for subcutaneous administration is approved for the stimulation of follicular development in women with severe LH and FSH deficiency.[17] Lutropin alfa was shown to promote optimal follicular development in hypogonadotropic hypogonadal women in clinical trials, and was generally well tolerated. In addition, lutropin alfa with follitropin alfa may also be beneficial in certain subgroups of normogonadotropic women (e.g. those with an inadequate response to prior follitropin alfa monotherapy, those aged ≥35 years and those with profound LH downregulation or who required excessive exogenous follitropin alfa).

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