

Clinical Experiences of Integrating the Follistim Pen® for the Self-administration of Follitropin Beta into Ovarian Stimulation Treatment Regimens

a report by

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In the US, until 2004 patients seeking ovulation induction (OI) or *in vitro* fertilization (IVF) treatments had to prepare and inject gonadotropins using a traditional syringe and vial method. Administering gonadotropins with the syringe and vial method is fairly advanced pharmacy, and asking patients—who are not professional pharmacists—to use this method proved stressful for the subjects involved.¹ Administration involved first the reconstitution of one or, more often, multiple vials of a lyophilized formulation. Once reconstituted and mixed, the medication would then be drawn up into a conventional syringe/needle for administration.

Whether for diabetics requiring insulin treatment or for infertility patients undergoing ovarian stimulation, the conventional syringe/needle system presents many issues for patients and their healthcare professionals (HCPs).²⁻⁴ For patients, acceptability of a medication relates to ease of use and convenience, impact on quality of life, and perception of the accuracy of dosing. For HCPs, concerns relate to tailoring the patient's dose to optimize treatment, accuracy and reliability, teaching time, and successful outcomes. Issues can include: nursing staff training for the administration of any kind of drug via syringe; patient concern about effective delivery via syringe necessitating further nursing staff training; pain at local delivery site; and wastage due to the need to mix the cakes and diluent. Patient issues also include: the need to ensure that no bubbles are present in the syringe; the fact that dosage increments are more difficult to adjust with the cake and diluent system; and that quality of life is significantly reduced.^{1,5,6} These issues have been addressed with the development of the Follistim® AQ

Cartridge (follitropin beta injection) and the Follistim Pen®. This pen delivery system is the first multiple-use device for the subcutaneous self-administration of a gonadotropin solution (in a cartridge). Taking its cue from the successes reported with pen devices developed for administering insulin to diabetics, this pen delivery system provides a user-friendly, viable alternative to the syringe and vial method.

Clinical Experiences

Patient Acceptability

Since its initial introduction in 2004, our clinical experience is that the Follistim AQ Cartridge for use with the Follistim Pen delivery system has been well accepted by patients undergoing IVF treatment and OI; this acceptance has been observed both for patients who have previously used only a syringe and vial method and for those undergoing treatment for the first time. Clearly, it is important for an infertility patient to understand the pen delivery system in order to be able to administer her correct dosages.⁷ The results of two multicenter open-label trials—one for ovulatory women undergoing controlled ovarian stimulation for IVF and the other for clomiphene citrate-resistant women undergoing OI—demonstrated that subjects understood how to use the pen device and how to correctly administer the desired dose (see *Figure 1, A and B*).^{8,9} Overwhelmingly, these two groups of patients rated their overall experience of self-administering using the pen device as “very good.”

As can be seen in the chapter by Mahony and co-authors (pages 23–26), patients and HCPs found that patients undergoing treatment with the Follistim AQ Cartridge and Follistim Pen found relief from many of the issues relating to medication preparation,^{3,4} including spillage (previously occurring with the syringe and vial method), bubbles forming through filling the syringe, and trouble with filling the syringe itself. While only 45.8% of patients were extremely or somewhat satisfied with the syringe and vial method, 95.4% of the patients were extremely or somewhat satisfied with the pen delivery system for self-administering. Our clinical experience since the pen delivery system became available has indicated that use of the system—loading the cartridge into the pen, setting the dial to the appropriate dosage, and administering the gonadotropins subcutaneously—is simple. Further, any patient issues can be addressed during the initial consultation period, although from clinical experience these tend to be few in number.^{7,10}

With the syringe and vial method, there were many more steps involved in terms of reconstituting, mixing, and administering the medication. It was found that initial use of the pen device removed many of these steps, as well as removing opportunities for human error.⁷ This is especially important when one considers that when using a conventional syringe/needle for self-



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injecting insulin, 60–80% of diabetics have been estimated to perform some aspect of the administration process incorrectly.^{11,12}

Local Tolerance

A number of factors may influence the severity of injection site pain, including the injection volume, the speed of the injection, osmolarity, additives in the formulation, the injection site, and the size of the injection needle.⁶ Comparative studies have reported significantly less injection site pain with the Follistim Pen compared with conventional syringe/needle administration.^{6,13,14} In both registration trials, patients reported that administration of follitropin beta with the pen delivery system was very well tolerated.^{8,9} This excellent tolerability is most likely due to the small injection volume of a gonadotropin with the purity of a recombinant product (as small as 30µL, which equals 25IU) delivered through a 29-gauge, 13mm micro-fine needle.

Quality of Life

Few studies have systematically evaluated quality of life for patients undergoing assisted reproduction,^{15,16} yet products that simplify treatment processes and make them less intimidating and intrusive should improve quality of life. One study of 1,700 patients undergoing ovarian stimulation in France recently reported on the impact of gonadotropin injections on the daily life of patients by collecting their impressions at the time of treatment.⁵ The results of this study demonstrated that ease of manipulation was by far the easiest, and the mean time for drug preparation the lowest, with the pen device administering follitropin beta compared with the self-administration of gonadotropins in individual or multidose vials with conventional syringe/needle.

More general quality of life aspects also recorded good results for the Follistim Pen, with subjects responding that they were mainly not affected “at all” by repercussions on both private and couples’ lives (see Figure 2, A and B). This trend was also observed in a patient satisfaction survey that found that 92.6% (versus 54.9%) of patients rated the pen “excellent” or “good” in terms of being able to continue with daily activities and subsequent impact on quality of life.⁵

Integration into Treatment Regimens

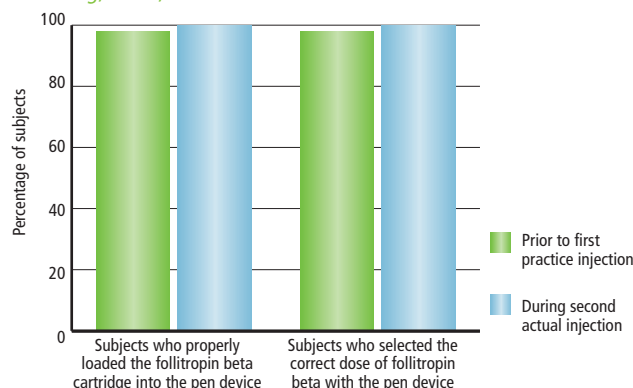
Results of the two registration trials mentioned above demonstrated that the pen device for the self-administration of follitropin beta is safe, effective, well-tolerated, and easy to use.^{8,9} Since this product became commercially available, our clinical experience has shown that the largest benefit of the Follistim Pen delivery system has been the ease of use for patient populations.^{1,7} Initial consultation sessions have proved effective and easy to understand for both patients and HCPs.

Integration into treatment regimens was similarly easy for both doctors and their nursing staff. The time spent introducing the system was greatly reduced compared with the syringe and vial method.⁷ As can be seen in the full Pen Pal Manuscript, this attribute was also reported in a survey of HCPs in which 83% of respondents agreed that the pen delivery system for self-administering follitropin beta required less teaching time. Specifically, HCPs observed that training using the pen device would take between five and 15 minutes compared with the conventional syringe/needle system, where training time was expected to be between 10 and 30 minutes.^{3,4}

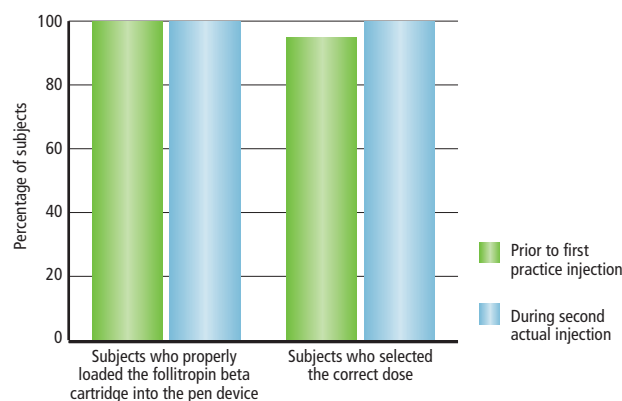
During drug development, a bioequivalence study was conducted that compared administration of follitropin beta as either a pre-mixed solution in a

Figure 1: Results of a Comprehension Questionnaire Evaluating Patient Understanding of Preparing and Administering Injections Using the Pen Device

A: In clomiphene citrate-resident women undergoing ovulation induction. Source: Pang, et al., 2003.⁸



B: In women undergoing in vitro fertilization. Source: Kettel et al., 2004.⁹



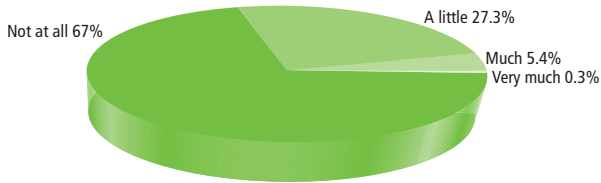
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cartridge via the pen delivery system or the lyophilized product via conventional syringe and needle.¹³ The results indicate that because the pen delivery system is a precision instrument delivering exactly the dose indicated, it delivers on average an 18% higher amount of follitropin beta due to injection losses associated with a conventional syringe/needle. The main noticeable outcome for equivalent dosages prescribed using the current pen device was higher patient response.^{1,7} These higher responses can be attributed to the pen delivery system, where the patients receive the full dose of medication prescribed. Conversely, with the vial and injections with needle and syringe, obligatory loss undoubtedly occurred. To educate HCPs about this increase in delivered activity and to enable them to integrate the pen delivery system smoothly into treatment regimens, a dose conversion table is provided in the prescribing information. Therefore, when administering Follistim AQ (follitropin beta) with the Follistim Pen, a lower starting dose for gonadotropin stimulation and dose adjustments during gonadotropin stimulation should be considered for each patient.

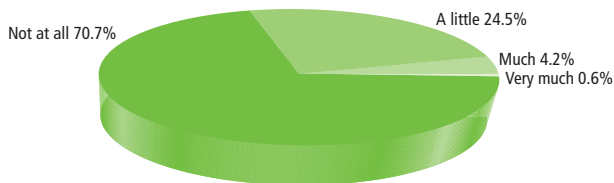
In clinical practice, the starting dose for initiating ovarian stimulation is optimized based on a series of prognostic criteria used to predict the expected patient response.^{1,7} This starting dose is individualized for each patient with the aim of ensuring the best possible response to gonadotropin stimulation while minimizing the risks of ovarian hyperstimulation syndrome (OHSS). We employed this practice for integrating the pen device into our clinical practice. Therefore, since our clinical experience is sufficient in this

Figure 2: Repercussion of Present Cycle

A: Impact on private life. Study = 1,089 patients



B: Impact on lives of couples. Study = 1,083 patients



Source: Sedbon, et al., 2006.⁵
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respect, the dose conversion table served as a guide. Subsequent dosage adjustments were easily made based on observed clinical responses for each patient. Due to the nature of its administration, this pen delivery system allows for this kind of flexibility.¹

Dosage Increments

This pen delivery system is the first pen device to enable precise and individualized dosing of follitropin beta from 50IU up to 450IU, in increments of 25IU.^{8,9,13} This is not practical or available using the syringe and vial preparation marketed in increments of 75IU. The pen delivery system allows gonadotropins to be administered according to patient need—i.e. a certain dose can initially be used, but then modified on a case-by-case basis. The other advantage of fine-tuning doses in 25IU increments is that this dosage is short-acting and can be adjusted easily.¹

There is great value in being able to tightly fine-tune a patient's treatment regimen, especially for women undergoing treatment for OI in whom lower starting dosages and smaller dose adjustments can help to prevent OHSS. This benefit is highlighted even further in younger patients and polycystic ovarian syndrome (PCOS) sufferers, who can be pushed into hyperstimulation and hyper-responsiveness leading to risk of OHSS or

SAFETY INFORMATION on Follistim® AQ Cartridge and Follistim® AQ Vial

- Follistim® AQ Cartridge/Vial, like all gonadotropins, is a potent substance capable of causing mild to severe side effects including ovarian hyperstimulation syndrome (OHSS), with or without pulmonary or vascular complications.
- Follistim® AQ Cartridge/Vial should be prescribed only by physicians who are experienced in infertility treatment, who should advise their patients of treatment risks, including OHSS and multiple births.

SAFETY INFORMATION on Follistim® AQ Cartridge

- Follistim® AQ Cartridge administered with Follistim Pen® delivers on average 18% more follitropin beta compared with lyophilized preparations administered with a conventional syringe and needle. A lower dose should be considered when using Follistim® AQ Cartridge.

multiple pregnancies if 50 or 75IU increments are administered.⁷ A recent report has confirmed our clinical experience.¹⁸ In this study, a low-dose step-up protocol with a starting dose of 50IU plus smaller dose adjustments in weekly increments of 25IU led to more controlled stimulation with a higher incidence of monofollicular development and ovulation, along with a lower cancellation rate due to hyper-response, while maintaining equivalent pregnancy rates and requiring a lower total dose of gonadotropin.

Conclusions

The two registration trials and subsequent studies show that patients and HCPs alike appreciate the convenience that the Follistim Pen device offers and prefer administration of gonadotropin with this novel delivery system compared with the syringe and vial method. Studies have also demonstrated that improved convenience translates into improved acceptability, quality of life, and patient compliance. It is therefore clear that the introduction of the Follistim AQ Cartridge and Follistim Pen have benefited both HCPs and their patients through its ease of use, acceptability, excellent local tolerability, ease of incorporation into treatment regimens, and significant clinical benefits experienced through use. ■

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