Expert Opinion

The redesigned follitropin α pen injector for infertility treatment

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Introduction: Treatment for infertility may require multiple drugs and complex dosing schedules. Available injection devices for patients who require regular injections during treatment are reviewed in this article, focusing on pen injectors used to self-administer recombinant human follicle-stimulating hormone (follitropin α). Following the introduction of the first and second follitropin α pen injectors in the last decade, a third pen injector with improved design for the administration of follitropin α has been developed for use in fertility treatment cycles.

Areas covered: This paper presents the results of the dose accuracy testing with this pen injector that was performed in accordance with international standards (EN ISO 11608-1:2000). This overview also provides an understanding of the key features of the redesigned pen injector that are of interest to healthcare professionals.

Expert opinion: The availability of an improved injection device for the delivery of follitropin α used during infertility treatment cycles of ovulation induction and assisted reproductive technology offers patients and healthcare professionals new treatment administration options. As fertility treatment cycles involve the use of several injectable gonadotropins, a standard device that could be used for all such treatments would simplify both the administration and the teaching of administration considerably.

Keywords: dose accuracy, follitropin α, *in vitro* fertilization, infertility, injection device, ovulation induction, pen injector, recombinant human follicle-stimulating hormone

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1. Introduction

The prevalence of infertility in couples around the world is estimated to be ~ 9% and of these about 56% seek medical fertility treatment [1]. Infertility may be caused by female factors (such as ovulation disorders and tubal pathology), male factors (such as sperm abnormalities), combined male and female factors, or unexplained reasons.

Ovulation induction (OI) is a useful treatment option for the WHO Groups I and II women with ovulatory dysfunction. This approach involves administration of clomiphene citrate or recombinant or urinary human gonadotropins (follicle-stimulating hormone (FSH) with or without luteinizing hormone (LH),

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Article highlights.

- Infertility treatment cycles may require multiple drugs and involve complex dosing schedules.
- For some conditions that require regular injections on a long-term basis, administration devices have been developed for the patient to self-administer their medications.
- The use of pen injectors for the administration of recombinant human follicle-stimulating hormone is state of the art compared with vials/ampoules with syringes and needles.
- A redesigned pen injector for administration of follitropin α solution has been developed to provide an improved delivery device.
- The pen has been designed to incorporate features suggested or supported during early development.

This box summarizes key points contained in the article.

or human menopausal gonadotropin (hMG)) with the intent to stimulate monofollicular growth, maturation and ovulation. Treatment is tailored according to the individual patient's response as assessed by measuring follicle number and size by vaginal ultrasound and serum estrogen levels. For OI, a commonly used regimen commences at 75 IU FSH per day [2]. Ovulation may be triggered using human chorionic gonadotropin (hCG).

Assisted reproductive technologies (ART), which include *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI), are more complex treatment options that involve multifollicular ovarian stimulation using recombinant human FSH (r-hFSH) or urinary gonadotropins (u-FSH or hMG). Common regimens use 150 – 225 IU r-hFSH per day [2]. A gonadotropin-releasing hormone analog, either agonist or antagonist, is often used in ART cycles to prevent a premature LH surge that would cause untimely follicular luteinization and/or ovulation. Final follicular maturation is triggered using hCG. Oocytes are collected on average 36 h after hCG administration in an IVF or ICSI cycle and fertilized for subsequent embryo transfer or cryopreservation. Therefore, in a typical ART cycle, a patient may use many injectable products during the stimulation period with different associated training for the use and administration of each product [3].

Infertility treatment cycles may, therefore, involve multiple drugs and dosing schedules as dose modifications may be required during an individual treatment cycle [3,4]. Depending on the patient's response to ovarian stimulation, the dose of r-hFSH may require titration to achieve optimal efficacy, while maintaining an acceptable safety profile, as development of an excessive number of oocytes increases the risk of ovarian hyperstimulation syndrome, a potentially serious adverse event [5,6]. Flexible dosing during controlled ovarian stimulation is a key aspect for optimizing treatment outcomes.

Harmonization of administration devices for the various gonadotropins used in fertility treatment may aid both healthcare professionals (HCPs) and patients.

2. Injector pen technology

2.1 The evolution of drug delivery devices

For many drugs given subcutaneously or intramuscularly, the conventional administration method involves using a syringe and a needle to inject the medication that is initially provided in a vial or ampoule. If the product is packaged as a lyophilized powder, it must first be reconstituted with the accompanying diluent by withdrawing the liquid from the vial and then gently injecting it into the vial containing the powder. Not surprisingly, reconstitution errors may occur during this step [7-9]. Following reconstitution, the patient must then withdraw the reconstituted product with the syringe and needle, and change the needle prior to injection.

For some chronic conditions that require regular injections on a long-term basis, delivery devices have been developed to help patients self-administer medications, for example, by providing automated methods of needle insertion and injection. To facilitate administration of daily injections, devices such as manual injector pens, auto-injector pens, needle-free and electronic devices have become available [10]. Manual injectors feature a dial that allows the dose to be set before the injection is given and are particularly useful when the dose administered must be adjusted frequently to meet the therapeutic goal. Auto-injectors are spring-driven systems that make the injection process easier by automatically injecting the drug from a prefilled syringe or cartridge and are often used when only a single dose of medication is administered (i.e., not daily administration).

Pen injectors (defined as medical devices intended for the injection of medicinal products from cartridges) are the most commonly used injection devices [11]. To date, most of the experience with pen injectors has been with diabetic patients who self-inject insulin. Pen injectors are now the preferred mode of insulin administration, as they have made the injection process easier, less painful and more convenient. This has resulted in increased acceptance of therapy and improvements in glycemic control [6,12-15]. In patient surveys, prefilled disposable insulin pen injectors received positive ratings for intuitiveness, instruction time, ease of use and acceptance [16,17], and a pen injector for a mAb scored well in terms of pain and time to inject [18].

2.2 The evolution of injection devices for infertility treatment

All gonadotropin products were first available only in ampoules or vials of lyophilized powder for reconstitution with the enclosed solvent and were administered via intramuscular injection using a syringe and needle. Indeed, the majority of these products, including all urinary gonadotropins, continue to be packaged as lyophilized powder with enclosed

solvent. Over the past decades, however, advances have been made both in the gonadotropin formulations available and in the methods of administration. For example, with the availability of gonadotropin formulations that can be administered subcutaneously, most patients are now able to perform their own injections after thorough training by their healthcare provider. r-hFSH was originally supplied as a lyophilized formulation only, in single or multidose vials, for reconstitution prior to injection using a syringe and needle; however, it is now also available as a premixed solution for use with pen injectors.

Two pen injectors for self-administration of r-hFSH are available: the GONAL-f®/GONAL-f® RFF (Revised Formulation Female) Prefilled Pen (Merck Serono S.A. – Geneva Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany), the current injection device that is prefilled with premixed follitropin α, ready-to-use and disposable, and the Puregon/Follistim Pen® (Schering Corp., NJ, USA; now merged with Merck & Co., Inc., NJ, USA), a reusable device, designed for use with premixed, prefilled loadable cartridges of follitropin β. Ovidrel®/Ovitrelle® (choriogonadotropin α, recombinant hCG, Merck Serono S.A. – Geneva) and Elonva® (corifollitropin α, Organon Laboratories Ltd (Merck, Sharpe and Dohme Ltd – Geneva), Herts, UK) are available in some countries for administration via a prefilled syringe. All of these injection devices have been introduced in the past decade.

There are several reports that infertile patients find pen injectors simpler and easier to use than other administration methods [19-23]. Use of a prefilled pen injector and needle, rather than a vial/ampoule with syringe and needle, requires fewer materials for drug administration, storage and transport. Pen injectors have been reported to be nurse-friendly [24], but are currently not available for the full range of gonadotropin products used throughout the entire fertility treatment cycle.

2.3 Development of a redesigned pen injector for administration of follitropin α

2.3.1 Design and features of the redesigned pen injector

The first two pen injectors for administration of follitropin α were approved in the US in 2004 and 2007, respectively [25]. The original device was modified with built-in, enhanced, patient-friendly features, including visually improved numbering on the dose-setting dial. Based on the positive experiences of patients and nurses with the modified follitropin α pen noted above, further improvements have been implemented to produce the redesigned pen injector that is described hereafter. During its development, 102 HCPs from six European countries (Norway, Denmark, Finland, Sweden, Switzerland and France) took part in a market research exercise designed to provide initial feedback on the proposed pen design and to assist with further design optimization. The survey involved group discussions and the completion of questionnaires by participants.

A positive reaction to the proposed redesigned pen injector and its functionality was obtained during the survey. Among the main attributes of the proposed pen (**Figure 1**), several features were discussed, including a dose display that shows only the selected dose and the return of the dose reading to zero after injection of the full prescribed dose. Other proposed features discussed were a magnifying window, to enlarge the dosing number and a fully transparent cartridge reservoir with graduated markings to assist the user in determining the amount of product left in the multiuse pen. As all of these features were considered to be improvements in terms of pen design, design refinements resulted in the inclusion of a magnifying glass lid to cover the dose window and graduated markings on the clear reservoir holder (i.e., the cartridge container) (**Figure 2**).

The functional features of the redesigned follitropin α pen injector have now been finalized and are further described below. The dose display indicates the selected dose number that is set by the patient when the pen is ready for injection; the display returns to zero when the full dose has been injected (**Figure 2B**). If the entire dose is not available for injection with the current pen (i.e., an incomplete injection would be given), the remaining amount that has not been delivered is visible in the dose display, thus indicating to the patient the remaining dose to be injected using a second prefilled pen.

Among the main features of the redesigned pen is the inclusion of small dosing increments. The pen injector will be available in three dose presentations, which deliver total doses of 300, 450 and 900 IU follitropin α. The selectable dose ranges for the three dose presentations of the pen injector are 12.5 – 300 IU for the 300 IU pen (corresponding to a volume of 0.02 – 0.48 ml) and 12.5 – 450 IU (corresponding to a volume of 0.02 – 0.72 ml) for each of the 450 and 900 IU presentations, all with dosing increments of 12.5 IU. As the patient administers her daily injections during her treatment period, the amount of follitropin α solution remaining in the pen after each use is displayed in the graduated, clear reservoir holder (**Figure 2A**), which indicates the approximate amount of product left in the pen (the graduated markings are not for use when setting the dose). The pen injector is designed so that it is not possible to remove the pre-installed cartridge filled with follitropin α, and the pen is intended to be discarded safely (in designated safety containers) when the cartridge is empty.

2.3.2 Dose accuracy testing

The international standard EN ISO 11608-1:2000 specifies requirements and test methods for pen injectors [11]. Dose accuracy requirements allow an absolute deviation of ± 0.01 ml from a target volume lower than 0.2 ml and a relative deviation of ± 5% from a volume equal to or larger than 0.2 ml. Taking into account the pen design and the concentration of the follitropin α solution for injection, the acceptable deviation of ± 0.01 ml corresponds to ± 6.25 IU of follitropin α solution

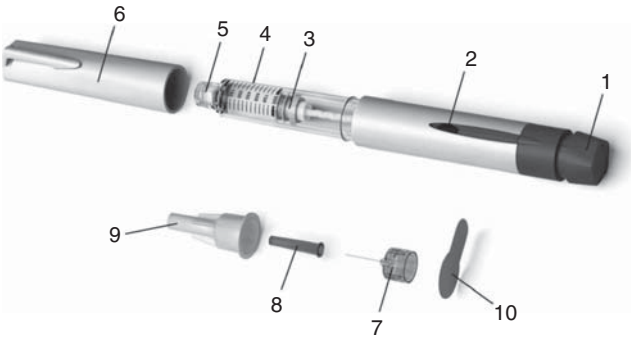

Figure 1. The components of the redesigned follitropin α/follitropin α RFF* pen injector. 1, Dose-setting knob; 2, dose display; 3, plunger piston; 4, graduated reservoir holder; 5, threaded needle connector; 6, pen cap; 7, removable needle; 8, inner needle shield; 9, outer needle cap; 10, peel-off seal tab. The pen barrel and cartridge are comprised of sections 1 – 5.

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*Revised Formulation Female.

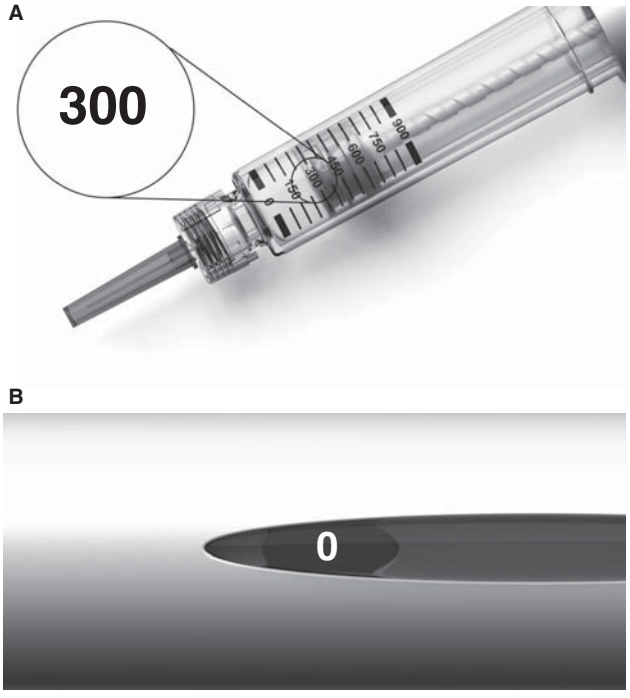

Figure 2. (A) The graduated scale on the clear reservoir holder shows the approximate amount of follitropin α remaining in the pen. **(B)** The dose display shows zero when a full dose has been administered.

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applicable to any target dose lower than 125 IU. For a target dose equal to or above 125 IU, the acceptable dose deviations are ± 5% of the selected dose.

Dose accuracy testing was performed with validation batches of all three redesigned pen injector presentations (i.e., 300, 450 and 900 IU). Depending on the pen dose presentation, four or five target doses distributed throughout the dose range were evaluated. For example, with the 900 IU pen, a minimum dose of 12.5 IU was tested, as were mid-range doses (75 – 237.5 IU) and a maximum dose (450 IU).

Table 1 summarizes the dose accuracy data for all selected doses tested (12.5, 75, 125, 237.5 and 450 IU) for the 900 IU pen presentation. As previously mentioned, 75 IU is a typical starting dose for patients undergoing OI for fertility

Table 1. Dose accuracy data for the different tested doses (12.5, 75, 125, 237.5 and 450 IU) for the 900 IU presentation of the redesigned follitropin α pen injector as obtained under normal conditions at room temperature.

Dose setting	900 IU pen (n = 60)				
	12.5	75	125	237.5	450
Lower/upper acceptance limits	6.3/18.8	68.8/81.3	118.8/131.3	225.6/249.4	427.5/472.5
Mean (s.d.)	12.2 (1.02)	72.4 (1.17)	122.8 (1.27)	234.9 (1.91)	455.5 (5.21)
Median	12.2	72.3	122.7	234.9	455.6
Minimum/maximum	9.9/14.4	70.1/75.3	120.1/125.4	230.5/238.5	440.3/465.6

All numbers are given in IU.
Lower and upper acceptance limits are set by EN ISO 11608-1:2000 [11] according to the dose tested.
IU: International unit.

treatment. The data presented here show that the 900 IU pen delivered the tested doses within the lower and upper acceptance limits, as determined by the ISO standards. Moreover, it shows that the 900 IU pen can accurately deliver a wide range of doses.

3. Conclusions

The redesigned follitropin α pen injector has been enhanced with several new features. Initial feedback on the pen design obtained from a pilot survey involving HCPs served to guide further design optimization. As a result, other desired features for the pen injector, such as a magnifying glass over the dose display and graduated markings on the cartridge reservoir that indicate the approximate units of follitropin α solution remaining in the pen device, were incorporated into the design. The redesigned pen injector also includes small dosing increments. As shown in the data included herein, dose accuracy was confirmed for the tested doses.

Patients undergoing fertility treatment often require multiple injectable medications, each with its own administration device. Learning the correct use of these devices may be a daunting task for some patients, increasing the burden of treatment. The possible availability of a standard injection device for the delivery of the different gonadotropin products used during OI and ART may be of interest to HCPs and patients in the future.

4. Expert opinion

Difficulties with conceiving children are associated with significant psychosocial consequences for many women and their partners [26,27], and the IVF treatment process itself is recognized as contributing to the physical, psychological and emotional burden on infertility patients. Thus, there is an unmet need for treatment approaches that lessen the burden of IVF and improve the overall patient experience. In a multinational, interview-based study involving 185 patients undergoing IVF and 170 physicians and nurse fertility experts, ovarian-stimulation treatment was considered by 55% (n = 102) of patients to impact on daily life, while 31% (n = 57) felt that daily injections limited their everyday activities [28]. Within the fertility expert group, almost half (47%, n = 80) expressed concern about whether their patients injected themselves correctly, with 26% (n = 44) raising concerns about patient compliance.

Women undergoing treatment for infertility may require a number of injectable treatments, but until the introduction of pen injectors for fertility treatment, injections were administered with vials requiring reconstitution and prefilled syringes only. The field has evolved over the past decade with the introduction of pen devices, developed to try to improve patient convenience and ease of use. Such devices may simplify administration and allow many patients to self-administer their gonadotropins at home. Self-injection can, however, be daunting to both patients and their partners, and they will naturally have many questions about how to administer these drugs. Consequently, a large proportion of consultation time is occupied by patients' questions about injection technique [23]. Providing education and training in the administration of injectable gonadotropin products can pre-empt many of these questions [23].

A device that is both easy to use and easy to teach should, therefore, be a useful option for both patients and HCPs. In nurse-led training on administration of FSH, of the participants (n = 123) who expressed a preference for an r-hFSH delivery method, 93.7% preferred to use a pen device rather than a needle-free reconstitution and conventional syringe method [23]. The most common reasons given for selection of a prefilled pen were that it was considered to be easy to use and had a simple and reliable dosing mechanism.

Nurses perceived advantages with two particular features of the redesigned follitropin α pen injector: a magnifying glass on the dose window, which helps to avoid potential dosing errors, and graduated markings on the clear reservoir holder of the cartridge, which serve to indicate the

approximate amount of follitropin α solution remaining in the device following injection. As fertility treatment cycles involve the use of several injectable gonadotropins, a standard device that could be used for all such treatments would simplify both the administration and the teaching of administration considerably.

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Declaration of interest

This study was sponsored by Merck Serono S.A. – Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany. M Christen and P Arriagada are employees of Merck Serono S.A. – Geneva. JC Schertz is an employee of EMD Serono, Inc. J Keitel and H Müller are employees of Haselmeier GmbH.

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