EXPERT REVIEWS

Insulin glargine and glulisine SoloSTAR® pens for the treatment of diabetes

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Insulin is an effective medication for lowering hemoglobin A_{1c} values and can be used for both basal and prandial coverage of hyperglycemia in Type 1 and Type 2 diabetes. Despite its effectiveness there is still reluctance by patients and physicians to add insulin into the treatment regimen for Type 2 diabetes when needed. One of the key barriers to initiating insulin therapy is the method of delivery. Insulin delivery pens are continually developed as a means to improve upon the vial and syringe and to make it easier for patients to incorporate insulin therapy into their lifestyles. The SoloSTAR® pen (Sanofi-Aventis, Paris, France) was developed to make insulin delivery easier and to help eliminate barriers to the initiation of insulin therapy. In this article, we discuss the features and characteristics of SoloSTAR that overcome existing unmet needs.

KEYWORDS: diabetes • hypoglycemia • injection force • insulin • insulin dose • SoloSTAR® pen

The increasing prevalence of diabetes in most populations has had a major impact on healthcare systems worldwide [1]. Global projections for diabetes are increasing at an alarming rate, with the total number of people with diabetes projected to rise from 171 million in 2000 to 366 million in 2030 [2]. In the USA for example, crude prevalence in 1999–2002 of total diabetes was 6.3% (19.3 million, 2002 US population), consisting of 3.5% diagnosed and 2.8% undiagnosed [3]. Currently, the prevalence of diabetes in the USA is approximately 7.0% (21 million people with diagnosed or undiagnosed diabetes) [101]. This rise in prevalence of diabetes is closely associated with an increasing prevalence of obesity across the globe (FIGURE 1) [2,4,5,102,103].

In healthy individuals, pancreatic β cells respond to changes in blood glucose by secreting insulin and increasing insulin synthesis. Diabetes is characterized by progressive β-cell failure, resulting in a decline in insulin secretion and hyperglycemia [6]. The therapeutic approach to diabetes commonly involves intensive insulin management (basal/bolus) to maintain normal glycemic levels, by replacing insulin as close to the physiological insulin secretion profile of healthy individuals as possible [6]. For patients with Type 1 or Type 2 diabetes, maintaining glycemic levels as close to the nondiabetic range as possible has been demonstrated to reduce the risk of developing diabetes-specific complications, including retinopathy, nephropathy and neuropathy [7–9]. Insulin is the most effective diabetes medication in lowering glycemia and, when used in adequate doses, can decrease any level of elevated hemoglobin (Hb)A_{1c} [10].

The recently published American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus statement guidelines recommend the early addition of insulin therapy in patients who do not meet target goals (BOX 1) [10].

Previous data from intermittent self-monitoring of blood glucose (SMBG) in Type 2 diabetes indicated higher contributions to elevated HbA_{1c} from fasting blood glucoses at higher levels (>9%), and significantly higher contributions to rise in HbA_{1c} from postprandial blood glucose (PPBG) at lower HbA_{1c} levels (<8%). More recent data from continuous glucose monitoring (CGM) systems indicate an inability for patients to achieve normal fasting blood glucose, even amongst those with near normal HbA_{1c} values (i.e., <6%; FIGURE 2) [11]. In addition, a significant contribution to rises in HbA_{1c} levels also comes from post-dinner elevations in blood glucose at higher HbA_{1c} values, which in turn might contribute to higher fasting blood

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glucose levels. Glucose variability, in part due to postprandial hyperglycemia, has been demonstrated to correlate with oxidative stress markers [12]. Recent data from CGM also indicates loss of postprandial glucose control preceding fasting hyperglycemia with increasing duration of diabetes (FIGURE 3) [13]. Thus, early focus on postprandial hyperglycemia may need to be considered (across all HbA_{1c} levels), especially when attempting to achieve normal fasting glucose.

Overview of the market: the impact of glucose control

Tight blood glucose control has been shown to prevent, or delay, the development of diabetes-related microvascular and macrovascular complications. An epidemiologic analysis of data from the United Kingdom Prospective Diabetes Study (UKPDS) patient population demonstrated that for each 1% reduction in mean HbA_{1c}, there was a 37% reduction in risk for microvascular complications alongside a 14% reduction in macrovascular complications [14]. Similar data from the Diabetes Control and Complication Trial (DCCT) in Type 1 diabetes shows the benefits of intensive insulin therapy resulting in significant reductions in both microvascular and macrovascular complications. Despite all of the available data, only approximately 30% of patients with Type 2 diabetes are on some sort of insulin treatment in the USA [15,101]. While this is, in part, due to some patients being well controlled with lifestyle management and oral antidiabetic drugs (OADs), patient and physician reluctance to start insulin therapy is also thought to be a contributor [16,17]. In order to achieve and maintain tight blood glucose control, insulin use in patients diagnosed with diabetes should be an integral component of their management strategy. Most patients with Type 1 diabetes, and increasingly more patients with Type 2 diabetes, use two different types of insulins to provide basal and prandial coverage for hyperglycemia; however, many still use premixed formulations. Indeed, it has been estimated that premixed insulins account for 22% of the total volume of insulin sold worldwide [15]. Premixed insulin usually contains a rapid-acting insulin and an intermediate-acting insulin with an aim to mimic endogenous insulin secretion patterns [18]. However, the use of premixed insulins is declining as the use of basal and prandial insulin increases [15], which is in line with the ADA/EASD consensus guidelines that only recommend the use of premixed insulin after a patient is stabilized on insulin and if their mix ratio is close to one of the available premixed insulin ratios [10].

A basal insulin supply, such as insulin glargine (Lantus®; Sanofi-Aventis, Paris, France), which has a relatively constant and peakless delivery over 24 h [19], can provide the steady, low-level insulin that is constantly present in the circulation to cover preprandial and overnight fasting periods. This is supplemented with multiple preprandial injections of regular human insulin or rapid-acting insulin analogs, such as insulin glulisine (Apidra®; Sanofi-Aventis, Paris, France), which aim to normalize and maintain good glycemic control, reduced glucose variability and better HbA_{1c} values.

Box 1. Summary of the American Diabetes Association/European Association for the Study of Diabetes consensus algorithm for the management of Type 2 diabetes.

- Step 1. Lifestyle modification and meformin
  - Lifestyle modification and metformin at diagnosis
  - Titrate metformin to maximum effective dose over 1–2 months
  - Check HbA_{1c} every 3 months until <7%, and every 6 months thereafter
- Step 2. Intensify therapy
  - Add further medications within 2–3 months if HbA_{1c} remains >7%:
    - Insulin
    - Sulfonylureas
    - Glitazones
  - Choice of agent depends on HbA_{1c} level
  - Insulin is recommended if HbA_{1c} remains >8.5%

HbA_{1c}: Hemoglobin A_{1c}.
From [10].

Insulin administration

An important aspect of diabetes care and glycemic control is the delivery of insulin. The method by which insulin is administered has been shown to impact patient acceptability of insulin therapy and quality of life, and may serve as a key barrier to insulin initiation [20]. Previously, the predominant route of insulin administration for patients with diabetes was the syringe and vial. However, this method of administration has many disadvantages, including fear of injections [21,22], poor dose accuracy [23], lack of social acceptance [24], inaccuracy when self-mixing insulins [25] and possibly changing pharmacokinetics of both long- and rapid-acting insulins. While still an injection device, insulin pens help to overcome many of these barriers.

Since the introduction of the first insulin pen, NovoPen® (Novo Nordisk, AS Bagsvaerd, Denmark) in 1985, insulin pens have continued to improve in design and usability features and address many of the barriers associated with administering insulin using a syringe and vial. Precision and accurate dosing is crucial for patients with diabetes, particularly for those on complex treatment regimens. Previous studies have indicated that up to 80% of people with diabetes incorrectly administer their insulin when using a syringe [26,27]. Santiago *et al.* conducted a precision, accuracy and durability study of an insulin pen (NovoPen) that tested the pen at three preset doses under stress conditions (multiple thermal and vibration stress tests), which were intended to replicate daily use by patients [28]. The accuracy of the insulin pen was within 1% of the preset dose after the stress and endurance tests, and the precision of the pen devices were likewise high (delivery-dose relative error was at most 0.8% of the intended dose) after thermal stress, vibration stress, free-fall testing or 5-year endurance testing.

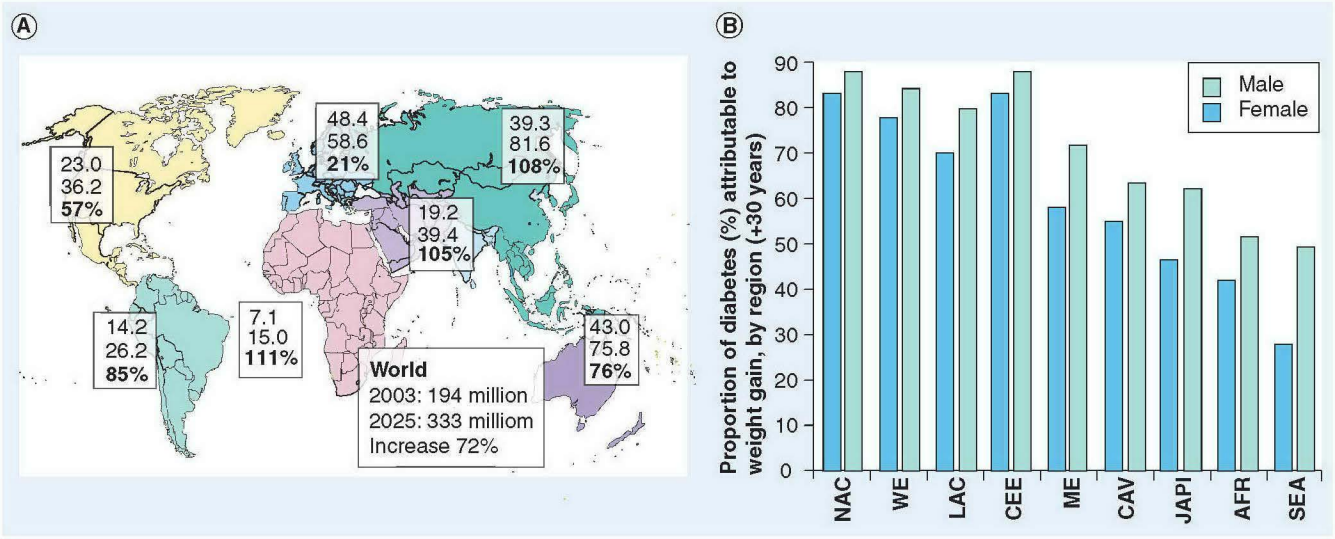

Figure 1. (A) Global projections for the diabetes epidemic; 2003–2025 (millions) and (B) increasing prevalence of obesity.
AFR: Africa; CAV: China and Vietnam; CEE: Central and Eastern Europe; JAPI: Japan, Australia and Pacific Islands; LAC: Latin America/Caribbean; ME: Middle East; NAC: North America/Cuba; SEA: South-East Asia; WE: Western Europe.
Part **(A)**: Reprinted with permission from Macmillan Publishers Ltd [1].
Part **(B)**: Information from [2,4,5,101,102].

Korytkowski *et al.* demonstrated that 82% of patients (n = 105) indicated greater confidence with dose setting using FlexPen® (Novo Nordisk) versus 11% of patients who preferred the syringe and vial method [29]. In addition, it was also demonstrated that 73% of patients reported more confidence in the accuracy of the dose delivered with FlexPen compared with 19% of patients using a syringe and vial. Insulin pens are now the predominant form of insulin administration in many countries, accounting for over 50% of insulin use worldwide, especially in Europe and Asia. In the USA uptake of insulin pens is steadily increasing, but it lags behind that seen in Europe and Asia [30].

Unmet needs

While insulin pen devices have made it easier for users to administer insulin, there remains scope for further development of insulin pens in response to unmet patient needs in relation to the development of SoloSTAR® (Sanofi-Aventis). Type 2 diabetes is characterized by obesity and insulin resistance and, coupled with the progressive nature of the disease, increasing doses of insulin are required over time. Accordingly, many patients need to administer doses of insulin exceeding 60 units, the maximum dose of many insulin pens, thus necessitating multiple injections. Limited joint mobility of the hand, commonly referred to as cheiroarthropathy, is frequently observed in patients with diabetes, particularly elderly patients, and is characterized by low grip strength and/or limited dexterity [31,32], which can impede the efficient administration of insulin, in such patients, using pen devices.

Problems with visual acuity are common in patients with diabetes and occur primarily as a result of diabetic retinopathy [33,34]. People with diabetes, particularly those with Type 1 diabetes, often use more than one type of insulin to manage basal and prandial insulin requirements, which can be provided by insulin glargine and insulin glulisine, respectively. The doses and pharmacodynamics of prandial and basal insulins differ; accordingly, it is important that the delivery devices are sufficiently differentiated to ensure low risk of users confusing the two insulin formulations. Patients with visual problems also place a greater reliance on non-visual modes when selecting dose. Dose setting and injections can be aided by audible recognition (the click sound), which occurs when a dose is dialed [35].

The SoloSTAR pen

An overview of the SoloSTAR pen & how it works

The continual evolution of insulin devices has led to the SoloSTAR pen, which is a prefilled, disposable insulin pen device designed for use once or several times daily. It is available for the administration of basal insulin glargine and prandial insulin glulisine for patients with either Type 1 or Type 2 diabetes, with two colors to differentiate the two pen devices. The insulin glargine SoloSTAR pen is approved for use in both the EU and the USA, whilst the insulin glulisine pen is approved for use in the EU.

The SoloSTAR pen is very easy to use. The user checks that they have the correct insulin pen. The user then attaches a new pen needle and performs a safety shot of 2 units to verify that the needle is working. The user then dials their dose and delivers the dose subcutaneously by pressing down on the injection button. The user will then remove the pen after counting to ten at the end of the injection to ensure the full dose is delivered. The needle is then taken off the pen and discarded safely. The pen cap is replaced and the pen can be stored until the next use. New, unopened

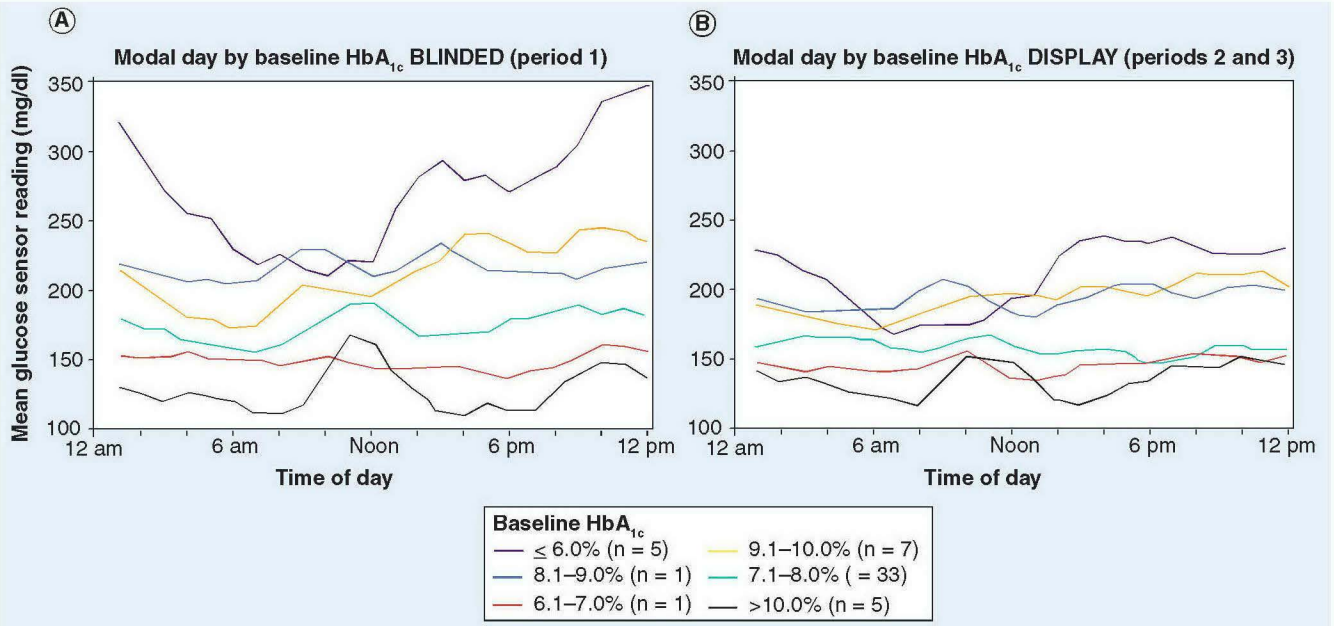

Figure 2. Modal day by baseline HbA_{1c} while subjects were blinded (A) to continuous glucose data or while subjects were given real-time access to continuous glucose values (B), trend graphs and high/low alerts.
Significant postpradial elevations in blood glucose levels were observed across all HbA_{1c} levels in both periods.

SoloSTAR pens should be kept in the refrigerator (2–8°C). Once opened, the SoloSTAR pen should be kept at room temperature for up to 28 days in accordance with storage condition recommendations, which differ in the EU (recommendations being below 25°C) and US (being below 30°C).

Evaluation of the SoloSTAR pen & responding to unmet needs

The SoloSTAR pen builds upon the strengths of current devices while including additional features, which have been ergonomically tested in order to establish their usability and effectiveness. Testing included collection of anthropometric data in intended user populations in order to recommend the most suitable user dimensions of the pen and develop the strength and robustness of the SoloSTAR pen, which compliments its user population.

Sensitivity & specificity

During development of the SoloSTAR pen, human factors were also considered, which led to a short-dial extension design facilitating easier grip during injection and enabling the user to administer even the maximum insulin dose with ease. This is an essential feature of the SoloSTAR pen when taking into account cheiroarthropathy, which is a significant problem in some patients with diabetes [31,32], with estimates that up to 58% of patients with diabetes have limited joint mobility of the hand [36] and significantly lower-grip strength compared with healthy controls [37]. The SoloSTAR pen has a maximum dose administration of 80 units, which exceeds the maximum dose of other available pens, except OptiClik (also 80 units), but including FlexPen and Lilly pen, which both administer a maximum of 60 units (Table 1). With higher doses of insulin required in obese patients especially with Type 2 diabetes, this is an important feature of the SoloSTAR pen, as it enables higher dose users to minimize the number of injections required.

Also, under varying temperature conditions, the SoloSTAR pen successfully passed dose accuracy testing, ensuring consistent and reliable insulin dose accuracy in a laboratory setting (Table 2) [38]. Moreover, the measured dose accuracy of SoloSTAR, when used by patients in a clinical setting, was within the limits of the International Organisation for Standardisation dose accuracy standard [39]. This reassures patients that, when used correctly, the SoloSTAR pen will deliver the dialed dose, which facilitates the titration of insulin dose without an increased risk of hypoglycemia or hyperglycemia. Injection force testing was performed to measure the force and force characteristics required to dispense a known volume of insulin (40 units) within a 4-s time period (Table 3) [38]. Findings from these tests showed that the SoloSTAR pen's highly efficient drive mechanism translates into a lower injection force than that of the Flexpen and Lilly pen [38].

To facilitate the differentiation of the insulin glargine pen from the insulin glulisine pen and to avoid the mistaken administration of basal instead of prandial insulin, or vice versa, the SoloSTAR pen is manufactured in two different

Table 1. Features of the SoloSTAR®, FlexPen® and Lilly pen.

Device	Maximum dose (units)	Dose increments (units)	Insulin products that can be administered using each pen*
SoloSTAR® (Sanofi–Aventis)	80	1	– Insulin glargine (LANTUS®) – Insulin glulisine (Apidra®)
FlexPen® (Novo Nordisk)	60	1	– Insulin detemir (Levemir®) – Insulin aspart (NovoLog®) – NPH insulin (Insulatard®) – NovoMix® 30 (30% insulin aspart and 70% protaminated insulin aspart)
Lilly pen (Eli Lilly and Company)	60	1	– Insulin lispro (Humalog®) – NPH insulin (Humulin®) – Humalog Mix75/25™ (75% insulin lispro) protamine suspension, 25% insulin lispro) – Humalog Mix50/50™ (50% insulin lispro protamine suspension, 50% insulin lispro)

*Availability may vary.
NPH: Neutral protamine Hagedorn.

colors: grey for insulin glargine and blue for insulin glulisine. This makes the SoloSTAR pen the first disposable insulin pen device to differentiate in pen body color.

This feature was included after consultations and assistance from healthcare providers, who suggested it to further minimize any confusion between the two insulins, especially in patients with visual impairments (Figure 4). In addition, another difference between insulin glulisine and glargine SoloSTAR pens includes a tactile differentiation of a raised ring on the dose button of the insulin glulisine pen, and other differentiation features include different colors in the labels and packaging.

Cost–effectiveness

Results from a recent study demonstrated that, in patients with Type 2 diabetes treated in a managed care setting, conversion from insulin injection with a syringe and vial to administration with an insulin analog pen device was associated with significantly lower annual treatment costs (US$16,359 vs 14,769, respectively; $p < 0.01$) as a result of improved medication adherence, fewer hypoglycemic events and reduced emergency department and physician visits [40]. These reductions could be as a result of the increased accuracy in dosing and timing of injection when using the insulin pen, which leads to a lower risk of hypoglycemia. Medication adherence was significantly improved after conversion to the insulin pen device (from 62–69%; $p < 0.01$).

A further potential cost saving for direct treatment could be made using pens when considering that insulin in vials is discarded by physicians after 28 days as per US FDA guidelines. Accordingly, insulin pens could be more cost effective for children and those taking small amounts of insulin. Since each insulin pen only contains 300 units, there will be less wastage, maintainance of biological activity of insulin and greater likelihood to follow the FDA label in clinical practice.

Recent results on the usability of the SoloSTAR pen reported by 65 healthcare professionals in clinical practice consider the SoloSTAR pen to be both easy to teach and easy to use for people with diabetes [41]. Of 65 healthcare professionals interviewed, most (n = 52; 80%) were able to spend less than 10 min training their patients to use SoloSTAR. This ease of use for both patients and healthcare professionals can translate into significant cost savings in relation to the time and resources spent training users of the SoloSTAR pen.

Use of the SoloSTAR pen in in-patient/hospital settings

In an in-hospital setting, the accuracy of the dose delivered is a key factor when selecting an insulin delivery system. This is because lack of accuracy may increase the risk of hypo- or hyperglycemia, jeopardizing patient welfare and in turn increasing diabetes-related treatment costs [38]. Used correctly, SoloSTAR pens will accurately administer the dialed dose of insulin, allowing reliable dose adjustment and minimizing the risk of resulting hypo- or hyperglycemia. In addition, color differentiation of the insulin glargine and glulisine SoloSTAR pens reduces the potential for hospital staff to confuse the two devices [38]. Furthermore, due to the ease of use, the introduction of insulin therapy in the hospital setting is easier with SoloSTAR pens than with traditional syringes and vials and this may result in patients being more likely to continue insulin therapy when discharged from hospital [38].

Clinical profile & post-marketing findings

Haak *et al.* recently conducted a preference study across four countries (US, Germany, France and Japan) involving 510 patients with Type 1 and Type 2 diabetes investigating the usability of the SoloSTAR pen, FlexPen and Lilly pen [42]. Patients were assessed on their ability to correctly perform a number of tasks involved in using each pen (including getting started and removing the cap, attaching a needle, setting and delivering a safety dose and dialing and delivering a 40-unit dose) and their preference of pens. The assessed steps for the SoloSTAR pen and FlexPen devices were correctly completed by a similar proportion of patients: 94% for the SoloSTAR pen

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