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REVIEW

NovoPen Echo® insulin delivery device

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Abstract: The introduction of insulin pen devices has provided easier, well-tolerated, and more convenient treatment regimens for patients with diabetes mellitus. When compared with vial and syringe regimens, insulin pens offer a greater clinical efficacy, improved quality of life, and increased dosing accuracy, particularly at low doses. The portable and discreet nature of pen devices reduces the burden on the patient, facilitates adherence, and subsequently contributes to the improvement in glycemic control. NovoPen Echo® is one of the latest members of the NovoPen® family that has been specifically designed for the pediatric population and is the first to combine half-unit increment (=0.5 U of insulin) dosing with a simple memory function. The half-unit increment dosing amendments and accurate injection of 0.5 U of insulin are particularly beneficial for children (and insulin-sensitive adults/elders), who often require small insulin doses. The memory function can be used to record the time and amount of the last dose, reducing the fear of double dosing or missing a dose. The memory function also provides parents with extra confidence and security that their child is taking insulin at the correct doses and times. NovoPen Echo is a lightweight, durable insulin delivery pen; it is available in two different colors, which may help to distinguish between different types of insulin, providing more confidence for both users and caregivers. Studies have demonstrated a high level of patient satisfaction, with 80% of users preferring NovoPen Echo to other pediatric insulin pens.

Keywords: NovoPen Echo®, memory function, half-unit increment dosing, adherence, children, adolescents

Introduction

The development of insulin injection pens has paved the way for easier, well-tolerated, and more convenient insulin regimens for patients with type 1 and type 2 diabetes mellitus (T1DM and T2DM), who have displayed a greater preference for insulin pens over standard treatment regimens.[1–3] When compared with multiple daily dosing with insulin therapy administered via a vial and syringe, insulin pens offer greater clinical efficacy, improved quality of life (QoL), and increased dose accuracy, especially at low doses.[3–5] Higher adherence rates have been reported with insulin pen use compared with vials and syringes.[2] Pen devices have also demonstrated reduced health care costs, with several studies reporting fewer hospital admissions due to hypoglycemic events and less insulin wastage.[2] Although it has been demonstrated that insulin pen devices are preferred by patients, vials and syringes are still widely used, even in industrialized countries such as the US.[6]

The first commercially available insulin pen, NovoPen® (Novo Nordisk A/S, Bagsvaerd, Denmark), was introduced in 1985. The NovoPen is a reusable injection

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device that comprises a disposable insulin cartridge and a syringe in a single entity, providing simple delivery of insulin compared with the vial and syringe treatment regimens.[5] The NovoPen family provides a comprehensive insulin delivery system using NovoFine®, NovoFine Plus®, and NovoTwist® needles and Penfill® insulin cartridges (Novo Nordisk A/S), enabling delivery of a range of insulin types.[5,7,8]

Each NovoPen was designed to deliver accurate doses of insulin. The insulin dose is set via turning the dial to the correct amount. Since the introduction of NovoPen 4, the user can also hear and feel clicks corresponding to dose increments. When the required amount of insulin has been set, the user inserts the needle subcutaneously and pushes the dose button to inject.[5] The needle length and gauge have been designed to reduce injection time and force, and therefore, reduce pain upon injection.[7] Other manufacturers of insulin device needles have also reported significantly reduced perceived pain and a patient preference for shorter needle lengths.[9,10] The simplified insulin administration system allows for a faster injection procedure with enhanced dose accuracy compared to vial and syringe.[4]

The portable and discreet size of NovoPen reduces the burden on the patient and improves the social acceptability of insulin injections, and is therefore likely to facilitate patients' adherence, leading to improvement in glycemic control, although this has proven difficult to directly demonstrate in clinical trials.[5,10,11]

Adherence is particularly important in adolescents and children, who have difficulties achieving good glycemic control. Unpredictable lifestyles, irregular eating patterns, pain upon injection, and the social stigma associated with injecting in public are the factors that make adhering to a particular treatment regimen challenging.[12–15] Children and adolescents also require a lower and more accurate dose of insulin to maintain good glycemic control due to their smaller body size. It is important for older children to begin to take responsibility for calculating doses and preparing devices for injection without appropriate guidance from parents and caregivers.[13] In addition, a simple lack of understanding of the consequences of missed injections and the effects of hyper- and hypoglycemia may affect adequate treatment. Specifically, prevention of hyperglycemia is of great importance in children and adolescents, whose ongoing cognitive and physical development places them at higher risk of complications.[16]

In 1989, soon after the introduction of durable insulin pens, the first disposable prefilled insulin pen, NovoLet® (Novo Nordisk A/S), was launched. When compared with vial and syringe regimens, prefilled insulin pens have many of the same benefits as durable insulin pens; they also further simplify the injection process by removing the insulin cartridge loading step.[1] The modern range of prefilled devices includes FlexPen® and FlexTouch® (Novo Nordisk A/S).

FlexPen has been rated by Japanese patients with T2DM, who were naïve to insulin devices, as simpler to use (77% vs 12%, $P<0.001$), easier to inject (67% vs 13%, $P<0.001$), and more convenient (71% vs 12%, $P<0.001$) than the OptiClik® Pen (Lantus , Sanofi, Bridgewater, NJ, USA).[17] These patients also indicated that they would prefer to use FlexPen (82% vs 13%, $P<0.001$) and trusted it to deliver insulin injections.[17] Technical features, such as end-of-dose confirmation click, large-dose display, and color coding to support differentiation of different insulin types, contribute to its increased usability and accuracy.[1] Health care professionals (HCPs) who had never prescribed insulin pens before rated FlexPen as easier to handle and more accurate compared with the conventional vial and syringe methods ($P<0.001$). Both experienced and insulin therapy-naïve HCPs found insulin pens to be more accurate than the vial and syringe methods (mean dose delivered ± standard deviation [SD], 9.91±0.11 U vs 9.82±0.25 U and 9.91±0.12 U vs 9.74±0.85 U, respectively).[18]

FlexTouch, the latest prefilled insulin pen, provides increased accuracy and ease of use over its predecessors. The spring-loaded injection mechanism results in a no push button extension and a lower injection force, ensuring an easier injection process.[1] A usability test performed in patients with impaired dexterity and cognitive function assessed FlexTouch and InnoLet®. In all categories of the usability questionnaire, FlexTouch was preferred to InnoLet, including the ease of use and the ease of learning to use the device.[19,20]

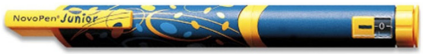
Since the release of NovoPen, a number of other insulin manufacturers have also introduced durable insulin pen delivery devices, including the HumaPen® range (Eli Lilly and Company, Indianapolis, IN, USA), and the OptiPen® Pro, OptiClik, and ClikSTAR® devices (all Sanofi, Bridgewater, NJ, USA).

Multiple generations of durable insulin pens comprise the NovoPen family, including NovoPen [1], 2, 3, 4, NovoPen Echo® and, most recently, NovoPen 5.[5,21] This study reviews one of the latest members of the durable insulin NovoPen family, the NovoPen Echo device.

The NovoPen family

The NovoPen family includes multiple generations of durable insulin devices (Table 1). Each new generation of pen builds

Table 1 Major technical changes in different versions of NovoPen® since 1985

NovoPen devices		Technical aspects/improvements
NovoPen® [1] (1985)		• Durable, reusable injection device with appearance similar to fountain pen • Combined insulin container and syringe in single compact unit • Utilizes disposable insulin cartridges loaded and removed from the pen by the patient
NovoPen® 2 (1988)		• Dose increments of 2 U • Maximum dose of 36 U • Allows required insulin dose to be "dialed" and set prior to injection • Displays previously administered dose
NovoPen® 3 (1992)		• Maximum dose of 35–70 U • Contains both dial and push button • Allows resetting of required dose without insulin waste
NovoPen® 1.5 (1996)		• Smaller 1.5 mL cartridge, making the pen shorter
NovoPen® 3 Demi (1999)		• Dose increments of 0.5 U
NovoPen Junior® (2003)		• Designed for pediatric population • Vibrant colors • Dose increments of 0.5 U
NovoPen® 4 (2005)		• Dose increments of 1 U • Maximum dose of 60 U • More discreet design • Reduced injection force • Larger dosing scale • Audible confirmatory dosing click • Safety feature, preventing selection of dose that is greater than amount of insulin left in cartridge
NovoPen Echo® (2010)		• Designed for pediatric population • Dose increments of 0.5 U • Memory function • Available in two colors; choice of skins is also available
NovoPen® 5 (2015)		• Features same as NovoPen® 4 • Memory function

Note: Images reproduced from © 2015 Novo Nordisk A/S.[5,21]

on the previous design, with the addition of technical features that are developed to increase ease of use, adherence, and patient QoL.[5,21]

The first NovoPen was launched in 1985, a novel insulin injection device comprising a disposable insulin container that could be loaded and removed by the user and a syringe in a single compact entity.[5] The NovoPen [1] was designed to look like a fountain pen and to provide patients with a discreet, portable insulin device that improved patients' QoL compared with previous vial and syringe methods. A new updated version of the NovoPen, NovoPen 2, was released in 1988. Building on the previous design, the new pen featured 2 U dose increments, with a maximum dose of 36 U. The NovoPen 2 also allowed users to set the dose prior to injection and display the previously administered dose.[22]

NovoPen 3 was launched in 1992. The maximum dose that could be administered at one time increased from 36 U with NovoPen 2 up to 70 U with NovoPen 3. In addition to the set and read dial feature of NovoPen 2, a push button to release the dose was introduced. NovoPen 3 is more economical than its predecessors, allowing resetting of the required dose without insulin waste. NovoPen 3 was followed by NovoPen 1.5 in 1996, which was designed to hold a smaller insulin cartridge, and the device was shorter in length than the NovoPen 3. Subsequently, in 1999, NovoPen® 3 Demi was released as the first member of the NovoPen family to introduce 0.5 U dose increments, allowing more precise administration of insulin. NovoPen Junior® was introduced in 2003; designed with vibrant colors, it was the first NovoPen developed specifically for pediatric patients with diabetes.[5,22]

NovoPen 4 was launched in 2005 with a more discreet design.[5] The injection force was reduced by 50% compared with NovoPen 3, as well as having a four times larger dosage scale display to increase ease of use for visually impaired

patients.[23] NovoPen 4 introduced an audible confirmatory dosing click. On comparison with a range of other durable insulin pens, the audible clicks of NovoPen 4 upon dose setting and dose delivery were determined to be a distinguishable feature.[24] NovoPen 4 also has an added safety feature that ensures a dose greater than the amount of insulin remaining in the cartridge cannot be selected.[5] A large post-marketing observational study of 2,018 patients with diabetes mellitus evaluated treatment satisfaction with NovoPen 4 compared with previous treatments, which included NovoPen 3 and OptiClik. Patients showed a significant preference for NovoPen 4, with a Diabetes Treatment Satisfaction Questionnaire score median difference of 4.0 between baseline and end-of-study scores ($P<0.0001$). More than 70% of patients found NovoPen 4 easier to set, read, correct the dose, and change the insulin cartridge compared with their previous device. In total, 84% of patients rated NovoPen 4 as easier to use overall, and 97.2% of HCPs would recommend it to other patients.[25]

The NovoPen Echo was the next addition to the NovoPen family. Launched in Europe in 2010, and in the US in 2014,[26] the NovoPen Echo was designed based on the needs of children and adolescents, and it replaced the NovoPen 3 Demi and Junior devices.[5] Young children are often more insulin-sensitive than adults, requiring smaller and more accurate dose adjustments. The NovoPen Echo is the first NovoPen to combine the accurate injection of 0.5 U of insulin and a simple memory function.[27,28] Figure 1 demonstrates the NovoPen Echo memory function.[28] The function records the dose and time elapsed since the last injection, providing added security and reassurance for parents and other caregivers, such as school staff, that the insulin was administered at correct doses and times.[5,29] The memory function can also be used as a form of age-appropriate education to teach children the importance of dosing and timing of insulin injections, reinforcing the significance of taking their insulin medication correctly.[29] The size, weight, and additional technical features were designed to enhance ease of use, particularly in small hands (Table 2).[5,29,30]

NovoPen 5 is the latest member of the NovoPen family, launched in 2015. It combines the design and functionality of NovoPen 4 with the addition of the memory function of NovoPen Echo for use by adult/elderly patients.[21]

Method of insulin delivery and patient use

Treatment adherence can be compromised by fear of pain on injection. Pen-based injection systems have aided patients to overcome the fear of injection by reducing pain and discomfort. One possible reason for this is maintenance of the lubrication material on needles, which facilitates injections. When using a traditional syringe system, the lubrication material is often removed when inserting the needle through the insulin cartridge rubber stopper, creating a more painful injection experience.[15] The NovoPen family uses NovoFine, NovoFine Plus, and NovoTwist needles, which are specifically designed to address usability and patient comfort.[5,7,8] NovoFine needles have two caps: an outer needle cap and a second inner needle cap that also covers the needle.[7] In addition, they are very fine, short, and lubricated needles, reducing the painful bruising and bleeding that can be experienced with longer and thicker needles.[6,31–33] NovoTwist needles are designed to attach and detach NovoPen insulin devices using a twisting motion to increase the patient's ease of use.[8]

Young children often need small dose adjustments in their treatment as they are more insulin-sensitive than adults.[34] Elderly patients also require increased dosing accuracy, as

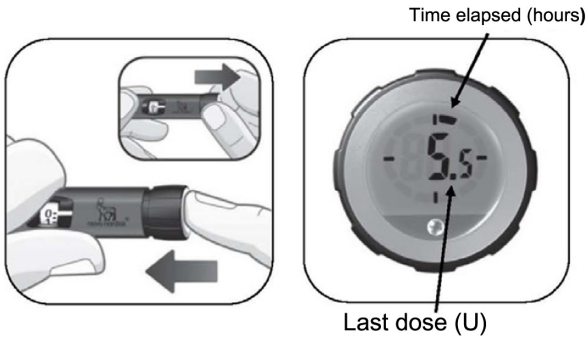


Figure 1 The NovoPen Echo® memory function.
Notes: Left panel: how to access the last dose information. Right panel: dose and time elapsed since last injection displayed on pen cap. Reproduced from Adolfsson P, Veijola R, Huot C, Hansen HD, Lademann JB, Phillip M. Safety and patient perception of an insulin pen with simple memory function for children and adolescents with type 1 diabetes – the REMIND study. *Curr Med Res Opin*. 2012;28(9):1455–1463,[28] reprinted by permission of the publisher (Taylor & Francis Ltd, http://www.tandfonline.com). Copyright © 2012.

Table 2 Technical and design features of the NovoPen Echo®

Memory function	Records dose and time since last injection for extra reassurance
Easy-to-use dial	• Dial will not select more units than left in the cartridge • Can be turned both backward and forward to correct mistakes and to minimize insulin waste
Easy to change Penfill® cartridge	Simply push back the piston rod with a finger tip
Half-unit increment dosing	From 0.5 U to a maximum of 30 U for fine-tuned dosing
Short button travel	Reduced injection movement makes it easier to self-inject
Stylish design	Available in red and blue with a choice of skins

they can have comorbidities or disabilities that exacerbate the difficulties of self-injection and increase the risk of dosing errors.[5] Newly diagnosed patients can enter a remission phase a few weeks after diagnosis; in this phase, their insulin doses need to be decreased and small dose adjustments are required.[34] The following three members of the NovoPen family of durable insulin pens allow for half-unit increment dosing adjustments: NovoPen 3 Demi, NovoPen Junior, and NovoPen Echo.

NovoPen Echo is among the durable insulin delivery pens that use two colors to help distinguish between different types of insulin, providing more confidence for both users and caregivers when administering basal and bolus types of insulin. Previously, this kind of distinction was only possible using different brands or models of pen. A study in which setting up, adjusting, and injecting with NovoPen Echo were performed by pediatric subjects, their parents, and HCPs found that 84% of participants successfully set up the device.[29]

Accuracy of insulin delivery and patient comfort

It is critically important for durable insulin pens to maintain their accuracy throughout their lifetime to ensure that the intended dose is delivered consistently. Underdosing or overdosing of insulin could lead to hyper- or hypoglycemia, respectively.[27] Historically, both insulin pen delivery devices and syringes have been demonstrated to be inaccurate when delivering small doses of insulin. Five new NovoPen 1.5, BD-pen® 1.5, and 30 U syringes were tested to determine the accuracy and reproducibility of delivering small doses of soluble insulin. Errors were highest for both pens and the syringe at the 1 U dose, with an error rate of 11% and 8% in the NovoPen 1.5 and BD-pen 1.5, respectively, and 23% in the syringe.[35]

Under conditions of failing dosing accuracy, changes in delivered insulin dose and glycemic control become unpredictable. The NovoPen Echo has been shown to successfully maintain dosing accuracy before and after simulation of 5 years of lifetime use under a range of environmental conditions and physical stress tests. Such challenges include preconditioned dry heat storage, cold storage, cyclical conditions, vibration testing, free fall, electrostatic discharge, and radiated field tests. Dosing accuracy before and after simulated lifetime use at doses of 5 mg remained similar under standard conditions (mean ± SD insulin dose, 5.31±0.69 mg and 5.82±0.63 mg, respectively), cool conditions (5.78±0.76 mg and 6.07±1.00 mg, respectively), and hot conditions (5.71±0.82 mg and 5.27±0.79 mg, respectively).[27] Moreover, when administering such small doses, accuracy is particularly important, as even minor deviations can have a substantial impact on glycemic control.[27]

Patient-focused perspectives

The use of insulin delivery pen devices has improved patients' QoL compared with vial and syringe systems by increasing lifestyle flexibility, convenience of use, and reducing pain.[5,14] A questionnaire to assess the attitudes of 54 patients with T1DM towards the NovoPen following 12 weeks of treatment determined that 63% of patients considered it to improve their lifestyle, 92% found it more convenient, and 58% reported less pain.[36] The development of pens with memory functions, allowing users to track their insulin history, is a technical feature that has been designed to increase usability.[21,37]

The multinational Diabetes, Attitudes, Wishes, and Needs (DAWN) Youth Web Talk Study strived to identify the challenges and issues for young people with diabetes mellitus using surveys for young adults (18–25 years), parents/caregiver of children (0–18 years), and HCPs caring for pediatric patients with diabetes mellitus. The study highlighted the poor management of diabetes mellitus in school-aged children, with six out of ten children not managing their diabetes mellitus successfully while at school.[29,38] A study by Burdick et al used data from insulin pumps to determine that children and adolescents are most likely to miss mealtime boluses, with as many as 65% of participants (n=31) missing ≥1 mealtime bolus per week. As few as four missed boluses per week can result in 1% increase in glycosylated hemoglobin levels.[39] One-to-one interviews conducted with a total of 205 children, parents, and HCPs to assess usability, functionality, and attitudes toward NovoPen Echo have demonstrated a high level of patient satisfaction. A total of 80% of participants preferred NovoPen Echo to other pediatric insulin pens.[29] It must be noted that, although NovoPen Echo recalls the dose and number of hours since the previous injection, it cannot determine whether a dose was actually delivered. For example, if the insulin flow is tested with 2 U, and the user does not proceed to inject insulin, the memory function will nevertheless save the dose and time of the insulin flow.[40]

Social acceptability

The discreet size of insulin pen devices, compared with vial and syringe regimens, has improved the social acceptance of diabetes mellitus management.[5] Insulin pens offer

convenience and flexibility, providing patients with the confidence to overcome issues of social embarrassment associated with self-injection, which in turn may lead to increased adherence to recommended insulin dosing schedules.[14] NovoPen Echo is highly rated in terms of design and appearance. During one-to-one interviews to assess usability, functionality, and attitudes toward the device on a scale of 1–6 (1= most favorable and 6= least favorable), 205 children, parents, and HCPs scored 1.71±0.79 (mean ± SD) for NovoPen Echo when compared with 2.02±0.93 for NovoPen Junior and 2.36±1.01 for HumaPen Luxura HD® (Eli Lilly and Company, Indianapolis, IN, USA).[29] The ability to personalize the pens with different skin designs has increased the willingness of children to inject in public, meaning they are less reluctant to use insulin pens while at school.[29] The range of skin designs is also beneficial to adolescents, because they are less likely to resemble a medical device.[29]

Usability and adherence

The Rating the Effects of Memory Function in Pediatric Insulin Devices (REMIND) study used questionnaires and case reports to examine the safety and memory function usability of NovoPen Echo and also the preference of users compared with their previous treatments in a routine clinical setting. A total of 354 patients with T1DM participated in the study. Patients reported a greater confidence in managing their insulin injections (73.3%) and were less likely to miss injections (85.9%). In comparison with their previous pen or syringe, a significant majority of patients preferred NovoPen Echo for its looks (75.7%), ease of push button depression (72.7%), ease of the fit of the pen in their hand (~50%), and use for injection (71.1%), as well as finding it easier to use overall (75.1%). Participants' preference-related results are summarized in Figure 2.[28]

Currently, few studies of the NovoPen family have measured treatment adherence directly; most rely on questionnaires or indirect evidence.[5] Adequate assessment of adherence is challenging and may require a combination of various techniques to gain a more comprehensive insight into patient behavior. In addition to self-reporting, nonself-reported measures, such as pill count-based approaches, dispensing/prescription refill data, and electronic monitoring, can be used. Although less convenient, regular assessment of plasma medication concentration, biological markers (eg, blood glucose), or direct observation can provide a more clinical approach.[41,42] Further studies are needed to demonstrate that a preferred delivery device leads to increased adherence in children and adolescents with T1DM.[43]

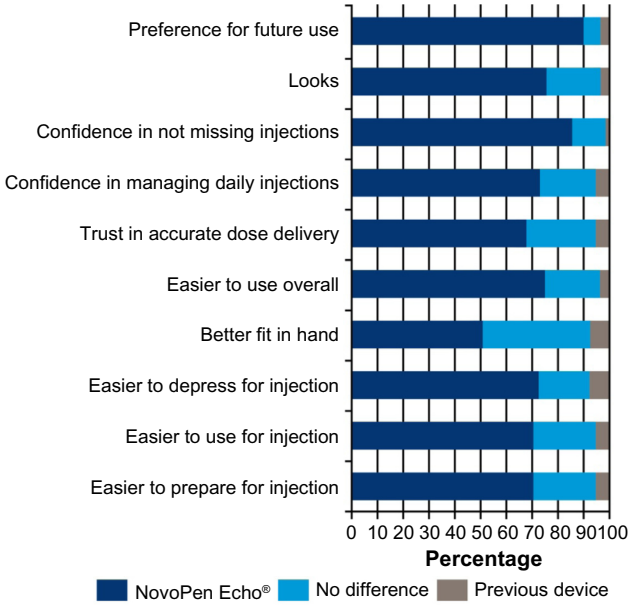


Figure 2 Patient preference for NovoPen Echo® compared with previous device.
Note: Reproduced from Adolfsson P, Veijola R, Huot C, Hansen HD, Lademann JB, Phillip M. Safety and patient perception of an insulin pen with simple memory function for children and adolescents with type 1 diabetes – the REMIND study. *Curr Med Res Opin*. 2012;28(9):1455–1463,[28] reprinted by permission of the publisher (Taylor & Francis Ltd, http://www.tandfonline.com). Copyright © 2012.

The clinical experience of many clinicians has highlighted a lack of adherence of patients to manufacturers' recommendations for insulin pen device use. Especially in young patients, there is a disparity between injection technique and manufacturers' guidelines, regarding the delay before withdrawing the needle after injection.[44] An expert panel has advised, on the basis of a systematic literature study investigating insulin injections, counting slowly to 10 before withdrawing the needle in order to deliver the full dose of insulin and prevent leakage.[45] This recommendation relies on an in vivo study that explored the leakage from six different insulin pens including the NovoPen 3 and NovoPen 1.5, after 1–7 seconds of needle hold-in time prior to withdrawal. The amount of insulin lost was variable depending on the pen used and the time of withdrawal. Eight of 20 NovoPen 3 devices showed insulin dribbling after 7 seconds of needle hold-in time, whereas none of the NovoPen 1.5 pens leaked after 7 seconds.[46] More recently, a study evaluated potential insulin under delivery in cases of premature needle withdrawal after injection with five prefilled insulin pens, including the aspart FlexPen, detemir FlexPen, and NovoPen Echo with aspart and detemir insulin cartridges. This evaluation also highlighted the importance of waiting before withdrawing the needle after an insulin pen injection to avoid under-delivery of insulin, which can represent up to one-fifth of the selected dose.[44]

Comparisons with other devices

To date, NovoPen Echo is the only pen designed for children and adolescents that combines both half-unit increment dosing and a memory function.[5] Other insulin pens designed for children and adolescents include the JuniorSTAR® and ClikSTAR by Sanofi. Similar to the NovoPen Echo, the JuniorSTAR pen and HumaPen Luxura HD also offer half-unit increment dosing, but NovoPen Echo in addition has a dial-back safety feature that allows correction of dose selection errors.[47,48]

Place in therapy

Treatment adherence among younger patients with diabetes mellitus is lower than that among adults, contributing to poor glycemic control and diabetic ketoacidosis.[49] The increased ease of use of insulin pen devices has likely improved adherence among young patients with diabetes, although this has proven difficult to directly demonstrate in clinical trials.[5,50]

NovoPen Echo has been designed to specifically enhance adherence and usability in a pediatric population (Table 2).[5,27,40] Children and adolescents usually have a greater need for precise and smaller doses.[29] The increased accuracy and audible end-of-dose click are technical features of the NovoPen Echo that could also benefit elderly patients. Comorbidities such as visual impairment and lack of motor coordination can cause dosing errors and impede self-injecting, thereby reducing treatment adherence. The half-unit increment dosing of NovoPen Echo could also aid insulin-sensitive patients, and patients with increased insulin sensitivity due to, eg, Addison's disease, hypopituitarism, chronic kidney disease, or chronic pancreatitis.[5,15,51]

Conclusion

NovoPen Echo has been specifically designed for the pediatric population, combining different child-friendly technical features. The half-unit increment dosing function provides the accurate dosing that is often needed in children, while the memory function also provides parents and caregivers with extra confidence and security that their child is taking insulin at the correct doses and times. The combination of features designed to enhance usability, and its lightweight and customizable design, make it suitable for both children and adolescents, and also other age groups who have a need for increased accuracy and half-unit increment dosing, such as the elderly and insulin-sensitive adults.

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Disclosure

All authors are employees and shareholders of Novo Nordisk A/S. The authors report no other conflicts of interest in this work.

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