NICE advice

MiniMed 640G system with SmartGuard for managing blood glucose levels in people with type 1 diabetes

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Summary

The MiniMed 640G integrated sensor-augmented pump therapy system with SmartGuard is a continuous glucose monitoring and insulin delivery system for people with type 1 diabetes. It can automatically suspend insulin delivery if blood glucose is predicted to drop below a pre-set level within 30 minutes. The available clinical evidence on the effectiveness and safety of the system is limited to 1 abstract, which reports a small, short-term prospective case series in which the sensor-determined glucose level did not reach a pre-set low limit in most predictive insulin suspensions. Two further proof-of-concept studies showed that the same algorithm as that used in the MiniMed 640G prevented hypoglycaemia both during night hours and during exercise. The MiniMed 640G system (insulin pump and transmitter) costs £3485 with additional consumable costs of about £400 per month.

The MiniMed 640G with SmartGuard is a new integrated sensor-augmented pump therapy system, which became available during the development of the NICE diagnostics guidance on integrated sensor-augmented pump therapy systems.

Product summary and likely place in therapy	Effectiveness and safety
• The MiniMed 640G system combines a continuous glucose monitor and insulin pump to automatically deliver insulin and maintain blood glucose levels within a pre-set range. • The system would be used by people with type 1 diabetes who have episodes of disabling hypoglycaemia despite optimal management with continuous subcutaneous insulin infusion.	• The available clinical evidence on the safety and effectiveness of the MiniMed 640G system when used with the SmartGuard predictive algorithm is limited. • One 4-week prospective case series of 40 patients (reported as a conference abstract) with type 1 diabetes assessed the ability of the MiniMed 640G to prevent hypoglycaemia, and its acceptability to users. In 83.1% (1930/2322) of the predictive insulin suspensions, the sensor-determined glucose level did not reach the pre-set low limit. The results from the patient questionnaire suggested that the patients found the system easy to use and helped them achieve better glucose control. • Two proof-of-concept studies of the algorithm incorporated in the MiniMed 640G system included a total of 32 patients. One randomised, controlled, crossover trial of 10 patients with type 1 diabetes (reported as a conference abstract) concluded that the algorithm could reduce overnight hypoglycaemia. Only 2 of 10 participants reached the pre-set blood glucose threshold when SmartGuard was on, compared with 9 of 10 participants when SmartGuard was off. One case series of 22 patients with type 1 diabetes showed that hypoglycaemia was prevented in 12 out of 15 patients during an exercise session.

Technical and patient factors	Cost and resource use
• The MiniMed 640G system incorporates a proprietary algorithm (SmartGuard) that predicts blood glucose levels. It is designed to reduce the need for frequent daily blood glucose measurements and manual insulin injections. • It can automatically stop insulin delivery if blood glucose is predicted to drop below a pre-set level within 30 minutes, and will restart delivery when glucose levels recover. • The MiniMed 640G became available during the development of the NICE diagnostics guidance on integrated sensor-augmented pump therapy systems. It differs from the MiniMed Paradigm Veo system mainly in having the automated stop and restart functions described above.	• The MiniMed 640G insulin pump costs £2995 and the transmitter and charger costs £490 (all excluding VAT). • Consumables including glucose sensors, infusion sets and insulin reservoirs cost around £400 (excluding VAT) per month.

Introduction

The NICE guidelines on type 1 diabetes in adults and type 1 and 2 diabetes in children and young people describe the prevalence, burden of disease, diagnosis and management of type 1 diabetes. The NICE diagnostics guidance on integrated sensor-augmented pump therapy systems states that some people with type 1 diabetes may experience 'disabling hypoglycaemia', which is when hypoglycaemic episodes occur frequently or without

warning. Integrated sensor-augmented insulin pump therapy systems are designed to improve glucose control. The MiniMed 640G was introduced during the development of the NICE diagnostics guidance, which makes recommendations on other integrated sensor-augmented pump therapy systems.

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

CE marking

The MiniMed 640G system is a class IIb medical device. The manufacturer, Medtronic, received a CE mark in January 2015.

Description

The MiniMed 640G system is an integrated sensor-augmented pump therapy system. It consists of a continuous glucose monitor and an insulin pump. The system uses a disposable glucose sensor (Enlite), which is inserted under the skin of the abdomen by the user using an automatic device supplied with the system, and secured with a small self-adhesive patch. It continuously measures glucose levels in the interstitial fluid, which lag about 15 minutes behind capillary blood glucose levels measured using a finger prick. The sensor is replaced at least every 6 days. The sensor is attached to a non-implanted transmitter (Guardian 2 Link), which sends the data wirelessly to the insulin pump or a stand-alone monitor. The transmitter is approximately the size of a 2 pence piece and lies almost flat against the skin. The insulin pump or monitor displays the glucose data on a screen and can plot trend-lines. The sensor readings are updated every 5 minutes.

The insulin pump, which weighs about 92 g and is 5.3 cm×9.6 cm×2.5 cm, can be clipped to a belt or be carried in a pocket. An insulin reservoir that can hold up to 300 units of insulin is fitted to the pump. An infusion set carries insulin from the reservoir to the body

through a subcutaneous catheter. The reservoir and infusion set are changed every 2 to 3 days. The pump delivers a continuous basal rate of insulin needed for normal body functioning. This is a personalised background level of insulin agreed between the user and clinician and accounts for approximately one-half of daily insulin requirements. The MiniMed 640G has 48 basal rates, from which the user can set up a personal daily basal pattern with different rates at various times of the day. Up to 8 of these basal patterns may be programmed, for example, to allow for different needs at weekends. More bolus insulin can be delivered by the user on demand through the pump controls to cover an expected rise in blood glucose levels, typically after meals. The system is waterproof, and designed to be worn continuously.

The MiniMed 640G system includes the proprietary SmartGuard algorithm, which uses data from the interstitial continuous glucose sensor to stop insulin delivery if hypoglycaemia, as defined by the user with a personalised pre-set low glucose limit, is predicted to happen within 30 minutes. The system automatically restarts insulin delivery when it is predicted that blood glucose levels will be above the pre-set low, within a minimum of 30 minutes and a maximum of 2 hours from suspension. It is possible to set up to 8 suspend limits per day to account for individual lifestyles and meals. The MiniMed 640G is a further development of the MiniMed Paradigm Veo system, which only stops delivering insulin once hypoglycaemia is present, and automatically stays suspended for 2 hours unless manually turned back on.

The MiniMed 640G system provides information to the user by alarms, alerts or messages, depending in the seriousness of the problem. An alarm warns the user that insulin delivery is being prevented, for example, if the insulin flow is blocked or the battery needs replacing; alarms must be addressed straight away. An alert makes the user aware of a situation that may need attention, for example, a low insulin reservoir or a low battery. A message gives information about the status of the pump. In addition, the system gives alerts if sensor glucose levels are predicted to reach pre-set high or low levels in the next 30 minutes, or are rapidly changing. Users are notified of alarms and alerts using sound or vibration. A siren is sounded if an alarm is not cleared within 10 minutes.

Setting and intended use

The MiniMed 640G is intended for use by children and adults with type 1 diabetes who have difficulty managing their blood glucose levels by self-monitoring and multiple daily insulin injections. It is also designed for people who cannot easily identify hypoglycaemic events, have a history of severe hypoglycaemia, are susceptible to night-time

hypoglycaemia, or who fear daytime or night-time hypoglycaemia. Continuous glucose monitoring is not designed to completely replace conventional finger-prick tests but rather to give extra information on the direction (increase or decrease) and speed of blood glucose trends, and can be used to help guide therapy adjustments.

Current NHS options

Type 1 diabetes is currently managed by monitoring blood glucose levels and insulin replacement therapy. This usually involves multiple daily insulin injections, with the doses adjusted according to blood glucose levels, and planned meals and exercise. Healthcare professionals give education and training to support people using insulin.

The NICE guideline on the diagnosis and management of type 1 diabetes in adults recommends that continuous glucose monitoring is not routinely offered and should only be considered when standard management of blood glucose levels has not worked or been difficult. However, the NICE guideline for children and young people with type 1 diabetes recommends that children and young people who have severe hypoglycaemic events, or cannot recognise hypoglycaemic events or communicate about the symptoms of hypoglycaemia, should be offered continuous glucose monitoring.

NICE technology appraisal guidance on continuous subcutaneous insulin infusion for the treatment of diabetes mellitus recommends that insulin pump therapy be considered for adults and children aged 12 years and older if they have not been able to reach target glycated haemoglobin levels with multiple daily injections or have disabling hypoglycaemia. For children younger than 12 years, insulin pump therapy is recommended if multiple injections are impractical or inappropriate.

NICE diagnostics guidance on integrated sensor-augmented pump therapy systems recommends the MiniMed Paradigm Veo in selected patients and in specific circumstances (please refer to the published guidance for detailed information).

NICE is aware of the following CE-marked devices that appear to fulfil a similar function to the MiniMed 640G:

- MiniMed Paradigm Veo System (Medtronic)
- Vibe and G4 PLATINUM continuous glucose monitoring system (Animas and Dexcom).

The MiniMed Paradigm Veo System automatically suspends insulin delivery if glucose

levels fall to a pre-agreed level, however it does not predict when it is safe to restart insulin delivery. The user must manually restart insulin delivery or it automatically restarts after 120 minutes.

NICE is not aware of any other CE-marked devices that have a similar function to the predictive low glucose suspend and resume algorithm used by the MiniMed 640G system.

Costs and use of the technology

The MiniMed 640G system has the following costs (excluding VAT):

- MiniMed 640G insulin pump: £2995
- Guardian 2 Link kit (includes transmitter and charger): £490.

The Guardian 2 Link transmitter is compatible with only the MiniMed 640G insulin pump.

The consumables needed for the system cost (excluding VAT):

- Enlite glucose sensors (pack of 10): £525
- MiniMed Mio infusion sets (pack of 10): £109.50
- MiniMed insulin reservoirs (pack of 10): £29.50.

The MiniMed 640G insulin pump has a 4-year warranty, and needs 1 new AA (1.5 V) battery. Battery life is typically 7 to 14 days depending on the type of battery and the amount of use. The glucose sensors are replaced every 6 days, so each pack of 10 will last about 2 months. The infusion set and insulin reservoir need to be replaced at least every 3 days, so each pack of 10 will last about 1 month. The monthly cost of consumables is about £400 (excluding VAT).

People who use the MiniMed 640G will still need to have capillary blood glucose tests to calibrate the device to ensure the glucose sensor maintains its accuracy over time, and before changes in insulin therapy. A capillary blood glucose meter costs at least £15, and the test strips that are used with the meter cost about £20 for a pack of 50. Lancets for finger-prick blood tests cost around £10 per 100.

For people using continuous subcutaneous insulin infusion, several other manufacturers

produce continuous glucose monitors that do not link automatically to an insulin pump as well as pump systems with a range of specifications and functionalities. The pumps typically cost £2000–3000 with variable prices for consumables.

Continuous glucose monitors that do not link automatically to an insulin pump cost about £1000 for a transmitter and monitor, with extra cost for sensors.

People who inject insulin manually use an insulin pen that costs about £30 to £40. Needles for reusable insulin pens cost around £20 for a pack of 100. Most people have 4 blood tests and insulin injections per day, so the monthly cost of self-monitoring and injection is around £84, excluding the cost of insulin.

Likely place in therapy

The MiniMed 640G system would be used in place of other reactive continuous glucose monitoring and insulin pump systems when standard management of blood glucose levels has not worked or been problematic, according to the NICE guideline on type 1 diabetes in adults. NICE has produced diagnostics guidance on 2 other integrated sensor-augmented pump therapy systems for managing blood glucose levels, which recommends the MiniMed Paradigm Veo system as an option for managing blood glucose in people with type 1 diabetes if they have episodes of disabling hypoglycaemia despite optimal management with continuous subcutaneous insulin infusion. As with standard management, people using the system will still need to have regular consultations with their diabetes team, which may include consultants, nurses, dietitians and pharmacists, to ensure that the system is working satisfactorily.

Specialist commentator comments

One specialist commentator noted that although many people are satisfied with conventional insulin therapy or insulin pumps, there is a specific minority group of patients who have hypoglycaemic unawareness or recurrent disabling hypoglycaemia. This group meets the NICE criteria both for an insulin pump and for continuous glucose monitoring. Along with 2 other specialist commentators, they agreed that the MiniMed 640G system may be appropriate for this group of people. In addition, 1 specialist commentator has found the system useful for reassuring families when nocturnal hypoglycaemia is feared, and for those with young children who find it difficult to recognise hypoglycaemia.

Two specialist commentators noted the importance of setting insulin rates and alarms to suit the individual needs of the person, and of regularly reviewing these settings. This is especially relevant for children because insulin needs change with growth and development. One commentator noted that if they are not reviewed regularly, people may ignore or switch off alarms.

One commentator pointed out that the system is complex and not an easy option compared with multiple daily injections. They highlighted the importance of assessing the person's motivation and knowledge of their diabetes management, and giving training.

All of the specialist commentators noted difficulties in adopting and using the MiniMed 640G system. One commentator reported that the Enlite continuous glucose sensor, which is part of the system, was not as accurate as the Dexcom continuous glucose sensor used with the Animas Vibe insulin pump, and the system could suspend insulin delivery when, in the clinician's opinion, it was not necessary; that is, when glucose levels were low but stable. They stated that rebound hyperglycaemia sometimes happened when insulin delivery was suspended for too long, while another specialist commentator noted that there is concern that the suspension of insulin administration could lead to loss of glycaemic control. One specialist commentator reported difficulties in adopting the system due to the cost and NHS restrictions, but in their limited experience, the pump with continuous glucose monitoring will help to prevent admissions for the small number of patients with severe hypoglycaemia or a lack of awareness and may therefore be cost effective.

One specialist commentator noted that the battery life seems very short compared with other pumps, which use lithium batteries that can last 2–3 months.

One specialist commentator noted that the evidence base is very limited. They added that the cohorts included in the studies were already using sensor-augmented pumps and so were self-selected as being able to use the technology. The commentator stated that use of such pumps requires the support of an experienced team, and it remains to be seen how they perform outside of the research environment.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

The manufacturer does not recommend the use of this product by people whose impaired vision or hearing does not allow full recognition of the pump signals and alarms.

Patient and carer perspective

Representatives from 3 diabetes charities, that is, Diabetes UK, JDRF and INPUT, contributed the following patient and carer perspectives:

- Hypoglycaemia is a major effect of intensive insulin therapy and can be a barrier to effective treatment of diabetes. The MiniMed 640G is the first step towards a fully automated insulin delivery system, which would be a tremendous benefit to people with type 1 diabetes and their carers.
- Many people with type 1 diabetes have a continuous fear of hypoglycaemia, and anything that can reduce or remove that fear is beneficial for their quality of life.
- Parents of children with type 1 diabetes often check their blood glucose during the night because of the fear of night-time hypoglycaemia. Those who use continuous glucose monitors with alarms find them very reassuring.
- For those people who have lost hypoglycaemia awareness, this type of technology can be a life saver. If a patient with type 1 diabetes is not conscious of their blood glucose level dropping, then a continuous glucose monitoring system that can provide an alarm for the user to take appropriate action is very beneficial. The added advantage of the MiniMed 640 system is that it can take action to prevent the hypoglycaemia happening, which is clinically beneficial because people who have lost their hypoglycaemia awareness can often regain it if they are able to avoid hypoglycaemia for a time. Preventing hypoglycaemic episodes in this group is therefore about more than just preventing seizures, fits and potential 'dead in bed syndrome', but could also improve quality of life and overall quality of care by helping people recover hypoglycaemia awareness.

- People with type 1 diabetes are very scared of the associated complications, particularly blindness, kidney failure and amputation. National Diabetes Audit data (Health and Social care Information Centre) show that the group most at risk is young men and women between the ages of 15 and 34 years, who are 4 and 6.5 times respectively more likely to die than their peers. This group also has the worst metabolic control. They really struggle to keep diabetes under control, often deliberately keeping their blood glucose levels much higher than recommended to avoid hypoglycaemia, but in so doing, risk having diabetic ketoacidosis. For these people, a system that can help prevent hypoglycaemia and very high blood glucose levels could have real benefits, including cost-saving benefits for the NHS in preventing diabetic ketoacidosis and the cost of complications.
- The benefits of using continuous subcutaneous insulin infusion and continuous glucose monitoring, especially with new technology such as the SmartGuard, are what many people with diabetes want. This is the first step in the move towards an artificial pancreas being available, allowing people with diabetes and their carers to lose some of the diabetes distress, which current systems cannot help with.

Evidence review

Clinical and technical evidence

Regulatory bodies

A search of the Medicines and Healthcare Products Regulatory Agency website revealed 1 Field Safety Notice (MHRA reference: 2015/009/028/292/033) for the MiniMed 640G insulin pump (MMT-1711 and MMT-1712).

This relates to a malfunction of the pump drive motors, which would result in a pump error message alarm notifying the pump user that insulin is no longer being delivered. Medtronic has identified the cause of the issue and it has been corrected in the current manufacturing of the MiniMed 640G. There have been no reported failures from customers as a result of this issue.

No reports of adverse events were identified from a search of the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE).

Clinical evidence

The search for evidence on MiniMed 640G insulin pumps identified 1 abstract that reports a case series study (Choudhary et al. 2015a). The manufacturer stated that 2 published studies and 1 further abstract reported on the predictive algorithm in the MiniMed 640G insulin pump (Buckingham et al. 2010; Danne et al. 2014, De Bock et al. 2014). The Buckingham et al. (2010) study was excluded because the insulin pump used was from a different manufacturer to that of the MiniMed 640G system. The study by Danne et al. (2014) and abstract by De Bock et al. (2014) were included as proof-of-concept studies.

The abstract (Choudhary et al. 2015a) reported findings from a multicentre prospective case series. The information presented was extracted from the full conference poster (Choudhary et al. 2015b; table 1), which has more detail than the published abstract. Forty patients with type 1 diabetes, including 24 adults and 16 children (aged 9–17 years), who had previously used sensor-augmented insulin pump therapy were included. This study assessed the performance of the MiniMed 640G, its ability to help prevent hypoglycaemia and its acceptability to users. The patients used the MiniMed 640G for 4 weeks.

There were 2402 evaluable pump suspension events, in which the insulin administration was temporarily stopped once glucose levels were predicted to reach a pre-set low glucose limit within 30 minutes. This was an average of 2.1 events per patient-day. Of the 2402 suspended events, 2322 (96.7%) were before the pre-set low was reached. In 83.1% of these, the sensor-determined glucose value did not subsequently reach the pre-set low limit. The results from the patient questionnaire suggested that the patients found the system easy to use and it helped them achieve better glucose control. There were 4 mild adverse events reported (2 skin reactions, 1 common cold and 1 urinary tract infection). A full report of this study has been submitted for publication but was not publicly available at the time this briefing was developed.

The study by Danne et al. (2014) reported a single-centre prospective case series evaluating the potential benefits of a predictive threshold suspend algorithm (presented in table 2). The predictive low glucose management (PLGM) system comprised a Paradigm Veo insulin pump and an Enlite glucose sensor connected to a MiniLink transmitter, with the algorithm installed on a Blackberry phone (Canada). Twenty two patients with type 1 diabetes were given an overnight intravenous infusion of human insulin and glucose. The next morning, they participated in an exercise session while having insulin by continuous subcutaneous infusion. The exercise session was continued for a maximum of 4.5 hours or until reference HemoCue blood glucose reached 80 mg/dl. The exercise session consisted

of up to 6 cycles of exercises, lasting between 15 and 30 minutes each, on a stationary bike or treadmill. A 30-minute predictive horizon with a sensor threshold of 70 or 80 mg/dl was used. The threshold was set at 70 mg/dl for 2 of the experiments (exercise sessions) when hypoglycaemia occurred because of rapidly falling glucose levels during exercise. The remainder had a sensor threshold of 80 mg/dl. Insulin was suspended for up to 120 minutes when sensor glucose was predicted to be at or below the threshold within 30 minutes. Hypoglycaemia was prevented in 12 of the 15 experiments in which the PLGM system was triggered and insulin suspended. Hypoglycaemia (defined as sensor glucose less than 63 mg/dl) was not prevented in 3 of the exercise sessions when the PLGM system was triggered. The system was not triggered in 1 of the experiments for 1 patient, but no information is given about this patient and the reasons for the system failure are not clear.

In another study assessing the SmartGuard algorithm (De Bock et al. 2014; presented as a conference abstract, table 3), 10 patients were given the PLGM system comprising a Veo insulin pump, Enlite glucose sensor, MiniLink transmitter, Bluetooth-RF translator and a smartphone with the algorithm installed. The study was a randomised, controlled, crossover trial but the information presented in the abstract is limited. Overnight hypoglycaemia was induced by increasing basal insulin rates by 180%. The parameters were set for pump suspension to occur when a sensor glucose level of less than 4.4 mmol/l was predicted to occur in 30 minutes. In the control arm (with SmartGuard off), the glucose level in 9 out of 10 patients fell below the pre-set 2.8 nmol/l threshold. When SmartGuard was on (the intervention arm), only 2 of the 10 patients' glucose levels reached the 2.8 nmol/l threshold.

Recent and ongoing studies

One ongoing or in-development trial on the MiniMed 640G system for type 1 diabetes was identified in the preparation of this briefing.

Trial NCT02130284: In-clinic evaluation of the PLGM system in adult and pediatric insulin requiring patients with diabetes using the Enlite 3 Sensor.

Costs and resource consequences

Type 1 diabetes affects over 370,000 adults and 26,000 children in the UK. Most people with type 1 diabetes manage their blood glucose levels by regular daily self-monitoring and insulin injections. A small number of people have problems maintaining the correct blood

glucose levels by self-administration of insulin therapy, and so are at risk of the severe complications associated with diabetes. Short-term complications of type 1 diabetes are hypoglycaemia and diabetic ketoacidosis, which is when the body starts to use fat as an energy source. The longer-term complications of type 1 diabetes, such as neuropathy, nephropathy, retinopathy and cardiovascular events, are related to hyperglycaemia. If automated continuous glucose monitoring and integrated insulin administration is shown to be a safe and effective option for these people, the incidence of complications associated with hypoglycaemia may be reduced, with associated cost savings for the NHS. There is no evidence that the MiniMed 640G system has any further benefit in reducing the risk of hyperglycaemia compared with any other pump systems.

Strengths and limitations of the evidence

The current evidence for the MiniMed 640G with the SmartGuard algorithm is limited to a single prospective case series presented in a conference poster. The conference abstract and associated poster (Choudhary et al. 2015a and 2015b) provided information on the ability of the MiniMed 640G to prevent hypoglycaemia. The authors reported a mean rate of 2.1 automatic suspend-before-low episodes per patient-day. Most (83%) of these events happened before the sensor glucose levels reached the pre-set low limit suggesting the potential of MiniMed 640G to prevent hypoglycaemia events. This study has limitations inherent to a case series design. For example, it presents only descriptive results and lacks a comparator group. Because the study is presented only in abstract and poster formats, full methodological details are unavailable, and so it is not possible to evaluate the quality of this evidence fully.

The study (Danne et al. 2014) and abstract (De Bock et al. 2014) evaluating the algorithm are informative, although they do not evaluate the full integrated system. These studies were included as proof-of-concept for the SmartGuard algorithm. The study by Danne et al. (2014) was a single-centre case series with no comparator group and merely presented descriptive results. It is not possible to evaluate the quality of the randomised, controlled, crossover trial by De Bock et al. (2014) because the study is only presented as an abstract.

Relevance to NICE guidance programmes

NICE has issued the following guidance:

- Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) (2016) NICE diagnostics guidance DG21
- Type 1 diabetes in adults (2015) NICE guideline NG17
- Diabetes (type 1 and type 2) in children and young people (2015) NICE guideline NG18
- Diabetes in pregnancy (2015) NICE guideline NG3
- Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (2008) NICE technology appraisal guidance TA151

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Appendix

Contents

Data tables

Table 1 Overview of the Choudhary et al. (2015b) poster

Study component	Description
Objectives/ hypotheses	To evaluate the MiniMed 640G system for usability and hypoglycaemia avoidance.
Study design	Prospective case series study. Patients used the system for 4 weeks, during which they had 4 phone contacts to assess compliance. Pump and sensor data were collected at baseline and at the end of the study, and treatment satisfaction questionnaires were collected at the end of the study.
Setting	Three centres in Europe (UK, Denmark and Spain).
Inclusion/ exclusion criteria	Patients with type 1 diabetes and previous experience with sensor-augmented pump therapy.

Primary outcomes	Rate of hypoglycaemia prevention.
Statistical methods	Not stated.
Patients included	Twenty-four adults (aged 43.8±12.0 [19–65] years) and 16 children (aged 13.4±2.5 [9–17] years) with type 1 diabetes and previous experience with sensor-augmented pump therapy. The mean±SD (range) baseline parameters for all patients were: diabetes duration, 17.2±13.1 years; HbA1c, 7.6±0.9%; and BMI, 23.5±3.9 kg/m^2. Female 45%.
Results	There were 2402 evaluable pump suspension events; 2.1 per patient-day. Of the 2402 suspended events, 2322 were suspend-before-low events. In 83.1% of the 2322 suspend-before-low events, the SG value did not subsequently reach the pre-set low limit. The overall mean±SD duration of an automatic pump suspension event was 56.3±9.5 minutes (median 58.0, IQR 49.2 to 64.2). The mean±SD lowest SG level after pump suspensions was 70.3±7.1 mg/dl (median 70.8, IQR, 67.3–75.0). Most evaluable pump suspension events (1645/2402=68.5%) happened between 08:00 to 22:00; 31.5% happened at night. Patients found the MiniMed 640G system and its automated features easy to use, and felt it helped diabetes management. There were 4 mild adverse events (2 skin reactions, 1 common cold, and 1 urinary tract infection).
Conclusions	Automatic insulin pump suspension as implemented in the MiniMed 640G system can help patients avoid hypoglycaemia, without increasing hyperglycaemia.
Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; IQR, inter-quartile range; SD, standard deviation; SG, sensor glucose.	

Table 2 Overview of the Danne et al. (2014) study

Study component	**Description**

Objectives/ hypotheses	To test the potential benefits of the predictive algorithm.

Study design	Prospective case series study. Participants were told to avoid rigorous physical activity (for example, gym activity, swimming, or running) in the 24-hour interval before hypoglycaemia induction. A variable overnight intravenous infusion of human insulin (0.5 unit/kg of body weight in 48 ml of 0.9% NaCl) was started after dinner to stabilise the fasting glucose level at 110 mg/dl (that is, stable between 90 and 140 mg/dl for at least 1 hour before the beginning of the experiment). The overnight intravenous fluid infusion rate (half isotonic glucose solution if the blood glucose level was below 300 mg/dl; 0.9% NaCl if above 300 mg/dl; both at 60–80 ml/kg/24 hours) and insulin dosing scheme (0.1 iU/kg/hour for glucose above 200 mg/dl; 0.05 iU/kg/hour for glucose of 150–200 mg/dl; 0.025 iU/kg/hour for glucose of 100–150 mg/dl; or no insulin for glucose below 100 mg/dl) depended on capillary blood glucose levels. Each person was given a predictive low glucose management system comprising a Paradigm Veo insulin pump and an Enlite glucose sensor (calibrated during the night and before the onset of exercise) connected to a MiniLink transmitter, with the PLGM algorithm installed on a Blackberry phone (Canada). The pump was pre-programmed to personal settings without adjustment. A 30 minute predictive horizon with a sensor threshold of 70 or 80 mg/dl was used. The threshold was set at 70 mg/dl for 2 of the experiments (exercise sessions) when hypoglycaemia occurred because of rapidly falling glucose levels during exercise. The remainder had a sensor threshold of 80 mg/dl. Insulin was suspended for up to 120 minutes when sensor glucose was predicted to be at or below the threshold within 30 minutes. Study pump insulin delivery was started 1 hour before the planned exercise was started. After a stable fasting blood glucose level was reached, the intravenous glucose/insulin was stopped in the morning between 06:00 and 10:00. Patients were on an exercise ergometer for a maximum of 4.5 hours or until reference HemoCue blood glucose, checked at least every 15 minutes, reached 80 mg/dl. Under specific circumstances, the exercise session was continued even if the blood glucose value reached <80 mg/dl when the patient had no symptoms and the ''upward trend arrows'' appeared in the display of the insulin pump, indicating the glucose level was increasing. The exercise session consisted of up to 6 cycles of exercises on a stationary bicycle or treadmill, each lasting between 15 and 30 minutes. Each cycle was followed by a rest period of between 5 and 15 minutes. This was

	followed by an observation period while fasting until 1 of the following occurred: the patient needed a glucose rescue (based on symptoms or a HemoCue blood glucose level of <40 mg/dl); the suspended insulin infusion was restarted after successful PLGM triggering; or the maximum observation time of 4.5 hours was reached. If the person's glucose level did not reach the target range of <80 mg/dl during exercise, they were invited to repeat the experiment after at least a 14-day interval or withdraw from the study.
Setting	Single-centre in Germany (Diabetes Centre for Children and Adolescents, Hanover).
Inclusion/ exclusion criteria	Eligible patients were aged 12–21 years (inclusive), who had been on CSII for at least 3 months before screening, had type 1 diabetes for more than 12 months, had a total daily insulin requirement of 0.6–1.2 U/kg/day, and had HbA1c levels of >5.8% and ≤12.0% at screening. People could not participate if they had experienced an episode of severe hypoglycaemia within the last 3 months before the experiment.
Patients included	Patients with type 1 diabetes having suspension of insulin on CSII, n=22.
Primary outcomes	Rate of hypoglycaemia prevention.
Statistical methods	Descriptive statistics.
Results	Data from only 16 patients were evaluated because the hypoglycaemic threshold during exercise was not reached in 6 people. In 1 of the patients, the pump did not suspend insulin delivery. Hypoglycaemia was prevented in 12 of the 15 successful experiments when insulin suspension was triggered using the PLGM system. The mean (±SD) SG level at predictive suspension was 92±7 mg/dl, resulting in a post-suspension lowest glucose level (by HemoCue) of 77–22 mg/dl. The suspension lasted for 90±35 minutes (range 30–120), resulting in an SG level at insulin resumption of 97±19 mg/dl.

Conclusions	The PLGM threshold setting of 80 mg/dl with a 30-minute predictive horizon resulted in successful hypoglycaemia prevention in nearly all of the valid experiments. The fact that no reactive negative effects on glycaemia occurred at the end of suspension emphasises the safety and feasibility of this approach.
Abbreviations: CSII, continuous subcutaneous insulin infusion; HbA1c, glycated haemoglobin; iU, international units; kg, kilogram; mg/dl, milligram/decilitre; ml, millilitre; n, number of patients; NaCl, sodium chloride; PLGM, predictive low glucose management; SD, standard deviation; SG, sensor glucose.	

Table 3 Overview of the De Bock et al. (2014) abstract

Study component	Description
Objectives/ hypotheses	To investigate the performance of SmartGuard during increased overnight basal insulin delivery.
Study design	Randomised, controlled, crossover trial. Patients were randomised to intervention or control nights with SmartGuard switched on or off respectively, before crossing over to the opposite arm at least 1 week later. Overnight hypoglycaemia was induced by increasing basal insulin delivery rates by 180%. SmartGuard parameters were set so that the pump would suspend insulin delivery when a sensor glucose of <4.4 mmol/l was predicted to occur within 30 minutes.
Setting	Not specified.
Inclusion/ exclusion criteria	Inclusion/exclusion criteria were not specified.
Patients included	Patients with type 1 diabetes, aged 13–40 years (n=10).
Primary outcomes	Lowest sensor glucose level (the intervention was stopped if glucose was <2.8 mmol/l).

Statistical methods	Descriptive statistics.
Results	When in the control group (SmartGuard off), the glucose level in 9 of 10 patients fell below the 2.8 mmol/l threshold. Only 2 of 10 patients reached the 2.8 mmol/l threshold when SmartGuard was on. In the other 8 patients in the intervention arm, the mean ± SD lowest glucose sensor level was 3.5 mmol/l (±0.75 mmol/l). For those patients whose glucose did not drop to 2.8 mmol/l, the mean rate of glucose fall before pump suspension was 1.0 mmol/l/hr (±0.52 mmol/l/hr). This was compared with a rate of 1.6 mmol/l/hr (±0.49 mmol/l/hr) in people whose blood glucose level dropped to 2.8 mmol/l. The mean glucose level when the pumps automatically restarted after suspension was 4.5 mmol/l (±1.2 mmol/l).
Conclusions	The authors concluded that SmartGuard has the potential to reduce overnight hypoglycaemia in patients on insulin pump therapy.
Abbreviations: n, number of patients; mmol/l, millimoles per litre; mmol/l/hr, millimoles per litre per hour; SD, standard deviation; SG, sensor glucose.	

Search strategy and evidence selection

Search strategy

1. The following databases were searched from inception to October 2015 using the keyword "MiniMed 640G": Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R); Embase (via OVID); Cochrane Library; CAB Abstracts; Web of Science's Science Citation Index.

2. The internet was searched using the above keyword.

3. ClinicalTrials.gov, WHO ICTRP, and Current Controlled Trials were also searched for ongoing trials.

4. Information provided by the manufacturer in supporting this briefing was checked to identify any further information.

5. The manufacturer's website was thoroughly investigated.

6. Information provided by the manufacturer was thoroughly checked for relevant studies.

Evidence selection

The inclusion criteria were as follows:

Population: adults and children with type 1 diabetes who currently use or may benefit from using an insulin pump.

Intervention: MiniMed 640G insulin pump.

Comparator: any integrated or non-integrated systems for the monitoring and delivery of insulin including pumps, continuous glucose monitoring, self-monitoring and subcutaneous injection.

Outcomes:

- number and frequency of hypoglycaemic events
- unplanned hospital visits
- variability in blood glucose levels
- glucose control as measured by HbA1c (glycated haemoglobin)
- adverse events
- technical failure.

Study type: published clinical studies. Proof-of-concept, bench-top or basic science studies were excluded. Non-English language studies were excluded.

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths

and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance**.

Development of this briefing

This briefing was developed for NICE by the Birmingham and Brunel Consortium. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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Declarations of interest

No relevant interests declared.

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