

APEG Submission to the Post Market Diabetes Products Review of Insulin Pumps

About APEG

The Australasian Paediatric Endocrine Group (APEG) is the professional body in Australia and New Zealand which represents those involved in management and/or research of children with disorders of the endocrine system including diabetes mellitus. The great majority of children with diabetes in Australia are under the clinical care of members of APEG. A key focus of our organisation is to promote and maintain the highest standards of diagnosis and treatment of paediatric endocrine disorders.

Introduction

It is well recognised that achieving and maintaining strict glycaemic control in patients with type 1 diabetes is essential for reducing the risk of microvascular and macrovascular complications including retinopathy, nephropathy, neuropathy and cardiovascular disease. Insulin pump therapy and multiple daily injections are both effective intensive insulin regimens to achieve this control. The evidence suggests, however, that in certain populations the insulin pump may be a more appropriate treatment option for delivering benefits, especially in paediatric patients. These include clinical outcomes such as improved glucose control with less variability, lower HBA1c levels, fewer episodes of hypoglycaemia, as well as quality of life improvements for both young patients and their families.^{1,2} Testament to this is that individuals with T1DM on insulin pump therapy in Australia tend to be younger patients, with almost one third under 20 years of age and the percentage of total pump use highest among children aged 5-14 years.²

Clinical Outcomes on Insulin Pump Therapy

Clinical Need

There is a clinical need for insulin pump therapy. While most individuals with type 1 diabetes can effectively manage their glucose levels with multiple daily injections, there are many who fail to achieve adequate glycaemic control with this method. A key reason for this is the inconsistent absorption and action of subcutaneously injected insulin, resulting in unpredictable fluctuations in blood glucose levels.³ In turn, these fluctuations are associated with increased HBA1c levels and hypoglycaemia. Another problem is that long-acting insulin doses cannot be altered after injection, for example, to manage increased blood glucose levels pre-breakfast in countering the “dawn phenomenon”. Other factors contributing to poor glycaemic control include errors with insulin dose adjustments and timing for meals and exercise, as well as non-adherence to the multiple injection regimen.³

Insulin pump therapy infuses rapid-acting insulin subcutaneously via an implanted canula at a slow basal rate 24 hours a day, which can be adjusted on demand or pre-set to change at any time. In addition to the basal rate are patient-activated boluses (insulin boosts) administered at meal times, supported by an on-board bolus calculator advising the appropriate insulin dose that factors in several variables such as carbohydrate intake, pre-meal / target blood glucose levels and insulin sensitivity.³

A practical advantage of insulin pump therapy is the ability to adjust insulin administration according to food intake and exercise or physical activity requirements, which otherwise can be a challenge in paediatric patients.

Glycaemic Variability

A major issue for type 1 diabetes patients is managing glycaemic variability, especially when unpredictable, which also correlates with an increased incidence of hypoglycaemia. Those with the greatest variability also tend to maintain the highest HBA1c level on multiple daily injections, most likely to avoid increasing the occurrence of hypoglycaemia in an attempt to gain control.^{1,3,4}

Insulin pump therapy can reduce both the within-day and between-day variability observed with insulin injections to improve glycaemic control – an effect thought to be related to the smaller subcutaneous insulin depot of about one unit at any time during basal rate infusion.^{1,3} Reducing glycaemic variability this way allows patients to lower their HBA1c without increasing the risk of hypoglycaemia.³

Insulin pumps also enable more flexible, pre-programmable basal insulin rates and extended-wave insulin profiles to reduce hyperglycaemia risk after fatty meals.³

Paediatric Outcomes

The consensus in the medical literature, as well as Australian and international evidence-based clinical guidelines in the management of type 1 diabetes is that insulin pump therapy provides clinically significant benefits for paediatric populations, including a clinically important reduction in HBA1C levels, fewer hypoglycaemia episodes, and improved quality of life.^{1,5-10} Among quality of life benefits are improvements in various cognitive measures including thinking, selective attention and working memory, as well as fewer mood-related symptoms and less behavioural problems reported by parents.¹

Reducing the risk of recurrent and severe hypoglycaemia, in particular, is important since this limits the achievement of tight glycaemic control in children and adolescents, as well as creates significant anxiety and emotional morbidity for patients and their families.¹¹ A further complication is impaired hypoglycaemia awareness, which increases the risk of severe episodes resulting in coma or seizure. Hypoglycaemia has also been associated with a decline in neurocognitive function in children with type 1 diabetes, especially where the condition has been diagnosed before 5 to 6 years of age.¹¹

However, a recent meta-analysis, which included 1,414 patients with type 1 diabetes among whom were over 600 children and adolescents from 10 studies, found a markedly reduced severe hypoglycaemia rate with insulin pump therapy compared with multiple daily injections that was four times lower and statistically significant.⁷

Importantly, a comprehensive health technology assessment involving 74 studies concluded that insulin pump therapy provides some advantages over insulin injections for both children and adults.⁸ Furthermore, a landmark one year, multi-centre randomised controlled trial study involving 156 children and 329 adults found a significantly higher percentage of both children and adults achieved the target HBA1c level of <7% with sensor augmented pump therapy compared with injection therapy.^{9,10}

Potential Harms

There is a theoretical higher risk of diabetic ketoacidosis if the insulin pump fails to deliver insulin, however in reality this has not been the experience. Today's pumps contain various alerts and alarms to warn of potential problems with insulin supply, and patients receive continuous education and support on their diabetes management and pump use, which also helps to lower the risk. Of further relevance is that among published 15 studies published on this issue, none reported a significant increase in the incidence of diabetic ketoacidosis during pump therapy, while three reported a significant reduction.¹²

Importantly, insulin pump therapy is not merely about wearing a device. In order for patients to gain maximum benefit from this treatment option, a multi-disciplinary team, comprehensive patient education and continuous follow-up is required.¹² It is when one or more of these factors are not present and/or there is poor adherence to necessary activities, e.g. monitoring blood glucose frequently, adjusting insulin doses for meal content and insulin sensitivity etc., that potential harms may arise.

Daily Activities

In addition to clinical benefits, a major advantage of pump therapy over insulin injections, is the practicality of using a pump outside of the home. This is why the medical literature, including clinical care guidelines, recommends insulin pump therapy for children and adolescents with type 1 diabetes without first having to fail adequate glycaemic control with injections.^{1,3,5,6} Indeed, multiple daily injections are often considered impractical or inappropriate at school, which adversely affects adherence where children are reluctant or unable to inject or require a parent to go to the school to administer a lunchtime bolus dose.¹ Children may also be restricted from various activities including school trips. In addition, adolescents can be challenging with issues such as non-adherence, changing activity and sleep patterns and insulin resistance, yet which pump therapy can often address.³

Insulin Pump Program

It is important that a range of treatment options exist for patients in the management of type 1 diabetes including pump therapy and multiple daily injections, which helps ensure individual needs for effective insulin delivery are being met. There is also clinical guideline consensus and a body of evidence supporting insulin pump therapy as an alternative practical option for children and adolescents where injections are not considered appropriate or would lead to adherence problems. In particular, insulin pump therapy is a first line option for patients experiencing high HBA1c values, marked glucose variability or severe hypoglycaemia while on an optimal insulin injection regimen.

For these reasons, it is imperative the insulin pump program not only continues for people up to 18 years of age, but is also made available for existing pump users who are transitioning into adulthood. This would help to ensure continuity of care with a treatment option deemed optimal for these patients compared with multiple daily injections.

Eligibility Criteria

Clinical and other eligibility criteria should be in keeping with those currently applied in assessing patient eligibility to access insulin pump consumables under the National Diabetes Services Scheme, which, in turn, are broadly consistent with the Australian clinical care guidelines for type 1 diabetes.^{5,13} The NDSS criteria are clear and, in our opinion, reflects best practice, allowing children, adolescents and adults access to pump consumables where there is a high need based on clinical and quality of life considerations.¹³

Broadening the Insulin Pump Program to include adults with type 1 diabetes is appropriate given the importance of maintaining continuity of care. Indeed, there is no evidence base for excluding adults from the Program. Furthermore, we note a recent AIHW report on diabetes care and resource use among young Australians aged up to 30 years, which identified suboptimal monitoring and management of their condition.¹⁴ With regard to glucose monitoring, the report found that only those using insulin pump therapy purchased enough blood glucose test strips to meet recommended daily monitoring requirements.¹⁴

Insulin Pumps and Cost-Effectiveness

The cost-effectiveness of different pumps available under the Insulin Pump Program depends on the patient population and specific capabilities of the pump. These range from insulin delivery and various supporting features, through to sensor augmented pumps that combine insulin supply with a real-time glucose sensor, allowing continuous glucose monitoring. The evidence suggests sensor augmented pump therapy allows patients to improve glycaemic control without increasing their exposure to hypoglycaemia.^{9,10,15} There is also a sensor augmented pump available with a "low glucose suspend" capability, which ceases insulin delivery when a minimum glucose level (preset) is reached to avoid hypoglycaemia episodes.

We are not aware of any published studies comparing the benefits and risks of different insulin pumps and their cost-effectiveness. However, there does appear to be consistency in the literature that the most appropriate and cost-effective use of pump therapy is in people with continued high HBA1c values (especially those who subsequently show a marked reduction) or disabling hypoglycaemic episodes with multiple daily injections (including the use of long-acting insulin analogues and adequate patient education).^{1,8,12}

The APEG appreciates the opportunity to provide comment to the Review.

Yours sincerely,



Clinical Professor Timothy W Jones on behalf of the APEG Clinical Diabetes Network

References

1. Pickup JC. Management of diabetes mellitus: is the pump mightier than the pen? *Nat. Rev. Endocrinol.* Online publication 28 February 2012; doi:10.1038/nrendo.2012.28
2. AIHW. Insulin Pump Use in Australia. Australian Institute of Health and Welfare 2012. Canberra, Cat. no. CVD 58
3. Pickup JC. Insulin-pump therapy for type 1 diabetes mellitus. *NEJM* 2012;366(17):1616-24
4. Bruttomesso, D. et al. In type 1 diabetic patients with good glycaemic control, blood glucose variability is lower during continuous subcutaneous insulin infusion than during multiple daily injections with insulin glargine. *Diabet. Med.* 25(3), 326–332 (2008)
5. Craig ME et al for the Australian Type 1 Diabetes Guidelines Expert Advisory Group. National Evidence based clinical care guidelines for type 1 diabetes in children, adolescents and adults, Australian Government Department of Health and Ageing, Canberra 2011
6. National Institute for Health and Clinical Excellence. Continuous subcutaneous insulin Infusion for the treatment of diabetes mellitus: review of Technology Appraisal Guidance 57. NICE technology appraisal guidance 151, London 2008
7. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med.* 2008 25(7):765-74
8. Cummins E et al. Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technology Assessment* 2010;14(11)
9. Bergenstal RM et al. STAR 3 Study Group. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med* 2010;363:311–320
10. Slover RH, Welsh JB, Criego A, et al. Effectiveness of sensor-augmented pump therapy in children and adolescents with type 1 diabetes in the STAR 3 study. *Pediatr Diabetes* 2012;13:6–11
11. Ly T et al. Impaired awareness of hypoglycemia in a population-based sample of children and adolescents with type 1 diabetes. *Diabetes Care* 2009;32(10):1802-1806
12. Bruttomesso D et al. Continuous subcutaneous insulin infusion (CSII) 30 years later: still the best option for insulin therapy. *Diabetes Metab Res Rev* 2009;25:99-111
13. Available at: <http://www.ndss.com.au/en/Products--Outlets/Insulin-pump-consumables/Eligibility-Criteria/> Accessed 12 Feb 2013
14. AIHW. Diabetes Among Young Australians Australian Institute of Health and Welfare Canberra Cat. no. CVD 59
15. Pickup et al. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self-monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ* 2011;343:1-14 doi: 10.1136/bmj.d3805