

Insulin Detemir

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

Insulin detemir is a long-acting basal insulin that has recently been licensed for the treatment of diabetes mellitus in adults. It is soluble at neutral pH but reversibly binds to albumin thus delaying its action.

Alternatives to insulin detemir include neutral protamine Hagedorn insulin (NPH also known as isophane insulin) and insulin glargine.

The manufacturer claims that insulin detemir has a more predictable action profile than existing NPH and glargine insulins, that it reduces the number of overall and nocturnal hypoglycaemic episodes and, reduces HbA1c and fasting plasma glucose to a greater extent compared to NPH insulin, and does not cause weight gain. The data available would seem to indicate that although some of these claims may be statistically valid their significance in clinical terms remains unclear.

In several comparative studies designed to demonstrate equivalence with NPH insulin in patients with type 1 diabetes, no significant improvements in HbA1c were seen with insulin detemir. None of these studies were adequately powered to investigate other outcomes such as weight changes or hypoglycaemia.

There are two studies that evaluate the use of insulin detemir in patients with type 2 diabetes. They have demonstrated that insulin detemir is comparable to NPH insulin.

Insulin detemir appears to be well tolerated with an incidence and pattern of adverse events similar to NPH insulin. The most commonly reported adverse events are hypoglycaemia and injection site reactions.

Currently insulin detemir is available at the same price as insulin glargine.

In a recent review of insulin analogues, The Drug and Therapeutics Bulletin states that further long-term well-controlled studies are required to establish the safety and efficacy of insulin detemir, but concluded on current evidence that it may be useful for patients with frequent severe hypoglycaemia or nocturnal hypoglycaemia.

Introduction

Insulin detemir is a long-acting basal insulin analogue licensed for the treatment of diabetes mellitus in adults. It is soluble at neutral pH but reversibly binds to albumin thus delaying its action.¹

Insulin detemir is administered once or twice daily in combination with meal-related short or rapid acting insulin depending on the patient's requirements. Alternatives to insulin detemir include neutral protamine Hagedorn insulin, (NPH, also known as isophane insulin), which is normally administered twice daily and insulin glargine, normally administered once daily.

Evidence

Seven trials have been identified comparing insulin detemir with NPH insulin, (detailed summary in Appendix II). Although randomised, they are restricted to open-label studies as the products are distinguishable; insulin detemir is a clear solution whilst NPH insulin is a cloudy solution. Most studies evaluated insulin detemir as a twice-daily regimen^{2,3,4,6} in combination with various short/rapid acting soluble insulins.⁵

The majority of studies are conducted over 26 weeks with one extension study continuing for one year.⁶ Of the seven trials, five studies evaluated efficacy in patients with type 1 diabetes,²⁻⁶ and two studies evaluated efficacy in patients with type 2 diabetes which used a once or twice daily regimen of insulin detemir or NPH insulin according to pre-trial requirements.⁷⁻⁸ Only one study with insulin glargine was identified but this was a pharmacodynamic study and was not designed to explore differences in safety and

Brand Name, (Manufacturer): Levemir, (Novo Nordisk)

BNF Therapeutic Class: 6.1.1.2 Intermediate and long- acting insulins

Licensed Indications: Treatment of diabetes mellitus in adults

Dosage and Administration: The dosage should be adjusted individually and administered sub-cutaneously once or twice daily into the thigh, abdominal wall or the upper arm.

Marketed: June 2004

Cost Comparisons: It is difficult to compare costs of different insulins due to differing patient requirements and differences in therapeutic equivalence. Given that the cost of both insulin detemir and insulin glargine is identical (£26 per 1000IU; £39 for 5x3ml cartridges or pre-filled pens) it is assumed that annual costs are comparable.

NICE, in their guidance on insulin glargine estimated that it costs £203 to treat a patient for one year with insulin glargine compared to £102 for NPH. It is therefore assumed that a similar cost differential would apply for insulin detemir.

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efficacy.⁹ All of these studies used change in HbA1c as the primary outcome measure.

Of the seven trials, five reported no significant difference in HbA1c changes between patients treated with insulin detemir and NPH insulin.^{2,5,6,7,8} Of the remaining studies, one reported a statistically significantly lower mean HbA1c with insulin detemir compared to NPH insulin (7.88% vs 8.11%, $p < 0.001$),⁴ whilst the other study, reported a significant decrease in HbA1c when two of the insulin detemir groups were combined and then compared to NPH insulin (mean difference -0.18% [-0.34 to -0.02], $p = 0.027$).³

The manufacturer refers to these latter two studies to support their claim that insulin detemir reduces HbA1c to a greater extent than NPH insulin. Other claims made by the manufacturer include a more predictable action profile, a reduction in the number of overall and nocturnal hypoglycaemic episodes, a reduction in fasting plasma glucose and no weight gain compared to NPH insulin. These outcomes have only been studied as secondary trial endpoints.

The seven trials have reported weight reductions in the range -0.3 to 0.9kg compared to increases with NPH insulin (range 0.1 to 1.6kg).

It is difficult to quantify the comparative effect of insulin detemir on nocturnal hypoglycaemia and fasting plasma glucose given the limited data available.

Safety

The Summary of Product Characteristics for insulin detemir states that, "Adverse drug reactions are mainly dose related and due to the pharmacological effect of insulin". Common adverse events ($>1\%$, and $<10\%$) include hypoglycaemia and injection site reactions. Uncommon adverse

events ($<1\%$ but more than 0.1%) include lipodystrophy, allergic reactions due to generalised hypersensitivity and refraction disorders.¹⁰

The overall incidence and pattern of adverse events in comparative trials with NPH insulin were reported to be similar.

Novo Nordisk initiated a 6-month post-observational study, last October. The study is non-interventional with the overall aim of evaluating the incidence of serious adverse drug reactions in an expected 25,000 enrolled patients.

Place in Therapy

The Drug and Therapeutics Bulletin has reviewed insulin analogues including insulin detemir. It does not advocate the use of insulin analogues as first line therapy for diabetic patients due to lack of long term safety and efficacy data which needs to be established. Also it states that there is little evidence to justify switching patients from their existing therapy to insulin analogues if they have adequate glycaemic control. However it recognises that these insulin analogues may be useful for patients with frequent severe hypoglycaemia or nocturnal hypoglycaemia.¹¹

In comparison with insulin glargine, there are very limited data to support the use of insulin detemir as a once daily regimen. However, insulin detemir has the advantage that it is easier to administer via the widely used Novopen 3 device whereas insulin glargine has to be administered using the less familiar Optipen or Autopen 24 devices. The Novopen device also allows the delivery of larger doses (up to 70 units of insulin in a single injection).¹²

Key Papers

2. Vague P, Selam JL et al. Insulin Detemir is associated with more predictable glycaemic control and reduced risk of hypoglycaemia than NPH insulin in patients with Type 1 diabetes on a basal bolus regimen with premeal insulin aspart. *Diabetes Care* 2003; 26(3): 590-596.
3. Home P, Bartley P et al. Insulin Detemir offers improved glycaemic control compared with NPH insulin in people with Type 1 diabetes. *Diabetes Care* 2004; 27(5): 1081-1087.
4. Hermansen K et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologica* 2004; 47: 622-9.
5. Russell-Jones et al. Effects of QD insulin detemir or neutral protamine hagedorn on blood glucose control in patients with type 1 diabetes mellitus using a basal-bolus regimen. *Clinical Therapeutics* 2004; 26: 724-36

Appendix I: Bibliography Appendix II: Table of Clinical Trials

Risk Management Issues:

The Summary of Product Characteristics states the following;

Insulin detemir should not be administered intravenously or used in insulin infusion pumps and intramuscular administration should be avoided.

Transferring patients from one type of brand of insulin to another should be done under medical supervision.

Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter.

Mixing of rapid acting insulin with insulin detemir should be avoided.

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Appendix I

Bibliography

References

1. Whittingham J, Svend H, Jonassen I. Crystal structure of a prolonged-acting insulin with albumin binding properties. *Biochemistry* 1997; 36: 2826-2831.
2. Vague P, Selam JL et al. Insulin Detemir is associated with more predictable glycemic control and reduced risk of hypoglycaemia than NPH insulin in patients with Type 1 diabetes on a basal bolus regimen with premeal insulin aspart. *Diabetes Care* 2003; 26(3): 590-596.
3. Home P, Bartley P et al. Insulin Detemir offers improved glycemic control compared with NPH insulin in people with Type 1 diabetes. *Diabetes Care* 2004; 27(5): 1081-1087.
4. Hermansen K et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologica* 2004; 47: 622-9.
5. Russell-Jones et al. Effects of QD insulin detemir or neutral protamine hagedorn on blood glucose control in patients with type 1 diabetes mellitus using a basal-bolus regimen. *Clinical Therapeutics* 2004; 26: 724-36.
6. De Leeuw et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes, Obesity and Metabolism* 2005; 7: 73-82.
7. Haak T et al. Lower within subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism* 2005; 7: 56-65.
8. Raslova K et al. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetics. *Diabetes research and clinical practice* 2004; 66: 193-201.
9. Heise et al. Lower within subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes* 2004; 53: 1614-20.
10. Levemir Summary of Product Characteristics. June 04. Novo Nordisk.
11. Anonymous. *Drug and Therapeutics Bulletin* October 2004; 42 (10): 77-80.
12. Ladva S. London New Drugs Group briefing. Insulin Detemir (Levemir) – a new basal insulin analogue. August 2004.

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Appendix II

Table: Key clinical trials of insulin detemir

Study	Trial Design	Trial Population	Primary outcomes
Vague P et al (ref 2)	26 week randomised phase III multicentre open-label comparative trial	448 patients with type 1 diabetes , diabetes duration 1 year, HbA1c <12%, BMI <35. 5 patients withdrawn from insulin detemir group and 5 patients from NPH group.	Mean HbA1c <ul style="list-style-type: none"> Twice daily insulin detemir (n=284), 7.6% Twice daily NPH insulin (n=146), 7.64% Difference = 0.04 (95%CI -0.218 to 0.128, p=0.61)
Home P et al (ref 3)	16 week randomised open-label parallel group study	408 patients with type 1 diabetes ; diabetes duration for >1 year, HbA1c <12%, BMI <35.5. 17 subjects withdrew.	Percentage reduction in mean HbA1c <ul style="list-style-type: none"> Twice daily insulin detemir (n=135), 0.82% (p=0.07) Insulin detemir every 12 hours (n=132), 0.85% (p=0.07) Twice daily NPH (n=124), 0.65% (p=0.07) Baseline adjusted ANOVA, p=0.082 Pooled insulin detemir groups (mean difference -0.18% [-0.34 to 0.02], p=0.027)
Hermans en K et al (ref 4)	18 week randomised (1:1) open-label parallel group study	595 patients with type 1 diabetes ; diabetes duration >1 year, HbA1c <12%, BMI < 35. 9 patients withdrew from insulin detemir group and 14 patients from NPH group.	Mean HbA1c <ul style="list-style-type: none"> Twice daily insulin detemir with insulin aspart (n=298) 7.88% (p=0.001) NPH insulin with Actrapid (n=297), 8.11% (p=0.001)
Russell-Jones et al (ref 5)	26 week randomised (2:1) open label parallel group study	747 patients with type 1 diabetes ; diabetes duration >1 year, HbA1c <12%, BMI = 25, on once daily basal bolus treatment. 17 patients withdrew from insulin detemir group and 15 patients from NPH group.	Percentage reduction in mean HbA1c <ul style="list-style-type: none"> Once daily insulin detemir (n= 491), 0.06% Once daily NPH insulin (n= 256), 0.06% Difference = -0.12% (95%CI -0.25 to 0.02, p=NS)
De Leeuw I et al (ref 6)	26 week randomised (2:1) open label parallel extension of earlier Russell-Jones D study.	316 patients with type 1 diabetes continued extension ; diabetes duration >1 year, HbA1c =12%, BMI = 35. 1 patient lost to follow up 5 patients withdrew from insulin detemir group and 3 patients from NPH group.	Percentage reduction in mean HbA1c <ul style="list-style-type: none"> Twice daily insulin detemir (n= 217), 0.64% Twice daily NPH insulin (n= 99), 0.56% No p values available
Haak T et al (ref 7)	26 week randomised open label parallel group study	506 patients with type 2 diabetes ; diabetes duration >1 year, HbA1c 7.85%, BMI 30.6. 34 patients withdrew – no further details available.	Mean HbA1c <ul style="list-style-type: none"> Once or twice daily insulin detemir (n= 315), 7.6% Once or twice daily NPH insulin (n= 155), 7.5% Difference = -0.16 (95%CI 0.003 to 0.312)
Raslova K et al (ref 8)	22 week randomised open label parallel group study	395 patients with type 2 diabetes ; diabetes duration >1 year, HbA1c <12%, BMI < 40. 10 patients withdrew from insulin detemir group and 6 patients from NPH group.	Mean HbA1c <ul style="list-style-type: none"> Once or twice daily insulin detemir with insulin aspart (n=195), 7.46% Once or twice daily NPH insulin with Actrapid (n= 199), 7.52% Difference = -0.062 (95%CI -0.249 to 0.125, p=0.515)