

## New Medicine Recommendation

### Insulin Detemir (Levemir®) for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above

#### Recommendation: Green

Appropriate for initiation and ongoing prescribing in both primary and secondary care. Monitoring is required but this is routine monitoring required for all insulins.

#### Summary of supporting evidence

- Insulin detemir is supported by the Scottish Medicines Consortium, which has reviewed and approved the drug. The support is restricted to patients unable to achieve good glycaemic control with established insulins.<sup>1</sup>
- NICE clinical guideline 17 lists insulin detemir as an option for adults with Type 1 diabetes<sup>2</sup>
- NICE clinical guideline 28 lists insulin detemir as an option for initiation in adults with type 2 diabetes if<sup>3</sup>
  - the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or
  - the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or
  - the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs
- NICE clinical guideline 28 lists insulin detemir as an option to switch to from alternative long acting insulins in adults with type 2 diabetes<sup>3</sup>
  - who do not reach their target HbA1c because of significant hypoglycaemia or
  - who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached or
  - who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or
  - who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections.
  - who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate.
- Two meta-analyses have compared basal insulin analogues (glargine and detemir) and neutral protamine Hagedorm (NPH) insulin in adults with type 1 diabetes. When detemir was compared with NPH, reductions in severe (RR 0.74, 95% CI 0.58 to 0.96) and nocturnal (RR 0.92, 95% CI 0.85 to 0.98) hypoglycaemia were observed, though there was no reduction in overall hypoglycaemia.
- On combining the eight trials that compared insulin detemir with NPH insulin, there was significantly less weight gain associated with the use of insulin detemir than NPH insulin (by 0.26 kg/m<sup>2</sup>, 95% CI 0.06 to 0.47).
- There was no reduction in overall hypoglycaemia associated with the use of basal analogues, though reductions in severe (OR 0.73, 95% CI 0.6 to 0.89) and nocturnal (OR

0.69, 95% CI 0.55 to 0.86) hypoglycaemia were observed.

- A 24 month RCT compared insulin detemir (n=331) with NPH insulin (n=166) as the basal insulin component of a basal bolus regimen. The reduction in HbA1c in association with insulin detemir was 0.22% (2.40 mmol/mol) (95% CI 0.41 (4.48) to 0.03 (0.33)).<sup>4</sup>
- One study showed greater patient satisfaction, though no change in quality of life, with the use of insulin glargine when compared with NPH.<sup>5</sup>
- In a 52 week study comparing insulin detemir and insulin glargine as the basal component of a basal bolus regimen in 443 patients with type 1 diabetes, there was no difference or change in HbA1c or rates of hypoglycaemia between the groups.<sup>6</sup>
- In a 26 week study comparing twice daily detemir with once daily glargine as part of a basal bolus regimen in 320 subjects with type 1 diabetes, there was no difference in improvement in HbA1c at the end of the study. There was no difference in overall confirmed hypoglycaemia, however, severe and nocturnal hypoglycaemia were 72% and 32% lower, respectively, with detemir. There was no significant difference in body weight.<sup>7</sup>
- In both children and adolescents, compared with NPH insulins, neither of the basal insulin analogues, glargine nor detemir, was associated with a significant difference in HbA1c.<sup>8</sup>

## Details of Review

<b>Name of medicine:</b> Insulin Detemir (Levemir®)
<b>Strength and form:</b> 100u/ml cartridge and pre-filled pen
<b>Dose and administration:</b> Subcutaneous injection.  Insulin Detemir can be used alone as the basal insulin or in combination with bolus insulin. It can also be used in combination with oral antidiabetic medicinal products and/or GLP-1 receptor agonists.  When Insulin Detemir is used in combination with oral antidiabetic medicinal products or when added to GLP-1 receptor agonists it is recommended to use Insulin Detemir once daily, initially at a dose of 0.1-0.2 units/kg or of 10 units in adult patients. The dose of Insulin Detemir should be titrated based on the individual patient's needs.
<b>BNF therapeutic class / mode of action:</b> 6.1.1.2 Intermediate and long acting insulins
<b>Licensed indications:</b> For treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.
<b>Proposed use:</b> for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

## Efficacy

<b>Scottish Medicines Consortium</b>  In its review (SMC 1126/16), the Scottish Medicines Consortium accepted insulin detemir (Levemir) <sup>1</sup> for restricted use within NHS Scotland for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above. The drug was restricted for use only in patients unable to achieve good glycaemic control with established insulins. The SMC did not publish an evidence review to accompany their approval.  Insulin detemir was previously accepted for restricted use by SMC in adults, adolescents and children from 2 years of age. <sup>9</sup>
NICE have produced 3 clinical guidelines for the treatment of diabetes with relevant sections, as follows: <b>NICE guidelines [NG17]</b> August 2015 Type 1 diabetes in adults: diagnosis and management <sup>2</sup>

## Long-acting insulin

1.7.3 Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. [new 2015]

1.7.4 Consider, as an alternative basal insulin therapy for adults with type 1 diabetes:

- an existing insulin regimen being used by the person that is achieving their agreed targets
- once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. [new 2015]<sup>3</sup>

1.7.5 Consider other basal insulin regimens for adults with type 1 diabetes only if the regimens in recommendations 1.7.3 and 1.7.4 do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost. [new 2015]

## NICE guidelines [NG28] December 2015 Type 2 diabetes in adults: management

### Insulin-based treatments

1.6.34 Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens:

- Offer NPH insulin injected once or twice daily according to need.
- Consider starting both NPH and short-acting insulin (particularly if the person's HbA1c is 75 mmol/mol [9.0%] or higher), administered either:
  - separately or
  - as a pre-mixed (biphasic) human insulin preparation.
- Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if:
  - the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or
  - the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or
  - the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if:
  - a person prefers injecting insulin immediately before a meal or
  - hypoglycaemia is a problem or
  - blood glucose levels rise markedly after meals. [2015]

1.6.35 Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes:

- who do not reach their target HbA1c because of significant hypoglycaemia or
- who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached or
- who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or
- who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. [2015]

1.6.37 Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. [2015]

**NICE guidelines [NG18]** August 2015 Diabetes (type 1 and type 2) in children and young people: diagnosis and management does not name insulin detemir as an option but does talk of the various classes of insulin therapies available.<sup>10</sup>

### **Insulin therapy for children and young people with type 1 diabetes**

While the insulin regimen should be individualised for each patient, there are 3 basic types of insulin regimen.

Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with 1 or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue.

Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula.

One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin.

1.2.18 Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen. [new 2015]

1.2.19 Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy as recommended in continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (NICE technology appraisal guidance 151). [new 2015]

1.2.25 Offer children and young people with type 1 diabetes a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences. [2004]

SIGN 116, which is a guideline on the management of diabetes,<sup>11</sup> provides a useful summary of the comparative efficacy of insulin detemir in comparison to other long acting insulins.

### **Basal insulin analogues in adults**

Two meta-analyses have compared basal insulin analogues (glargine and detemir) and neutral protamine Hagedorm (NPH) insulin in adults with type 1 diabetes.

The first meta-analysis, undertaken by the Canadian Agency for Drugs and Technologies in Health, concluded that use of glargine was associated with a reduction in HbA1c of 0.11% (1.20 mmol/mol) (95% CI 0.02 (0.22) to 0.21 (2.30)) while use of detemir was associated with a reduction in HbA1c of 0.06% (0.66 mmol/mol) (95% CI -0.13 (-1.42) to +0.02 (0.22)).<sup>12</sup>

Benefits in terms of hypoglycaemia were inconsistent. When glargine was compared with NPH insulin, there was no significant reduction in severe or nocturnal hypoglycaemia, however there was a high degree of heterogeneity between the studies. When detemir was compared with NPH, reductions in severe (RR 0.74, 95% CI 0.58 to 0.96) and nocturnal (RR 0.92, 95% CI 0.85 to 0.98) hypoglycaemia were observed, though there was no reduction in overall

hypoglycaemia.

In a further meta-analysis of 20 RCTs of greater than 12 weeks duration comparing basal insulin analogues with NPH insulin, the mean reduction in HbA1c associated with the use of analogues was 0.07% (0.77 mmol/mol) (95% CI 0.13 (1.42) to 0.01 (0.11)).<sup>13</sup> On combining the eight trials that compared insulin detemir with NPH insulin, there was significantly less weight gain associated with the use of insulin detemir than NPH insulin (by 0.26 kg/m<sup>2</sup>, 95% CI 0.06 to 0.47). Equivalent data were not available for glargine. There was no reduction in overall hypoglycaemia associated with the use of basal analogues, though reductions in severe (OR 0.73, 95% CI 0.6 to 0.89) and nocturnal (OR 0.69, 95% CI 0.55 to 0.86) hypoglycaemia were observed.

A 24 month RCT compared insulin detemir (n=331) with NPH insulin (n=166) as the basal insulin component of a basal bolus regimen. The reduction in HbA1c in association with insulin detemir was 0.22% (2.40 mmol/mol) (95% CI 0.41 (4.48) to 0.03 (0.33)). Risk of major and nocturnal hypoglycaemia with detemir was 69% and 46% lower respectively in comparison with NPH (p<0.001).<sup>4</sup>

One study showed greater patient satisfaction, though no change in quality of life, with the use of insulin glargine when compared with NPH.<sup>5</sup>

### **Comparison of insulin detemir and insulin glargine: Adults**

In a 52 week study comparing insulin detemir and insulin glargine as the basal component of a basal bolus regimen in 443 patients with type 1 diabetes, there was no difference or change in HbA1c or rates of hypoglycaemia between the groups. According to the study protocol, two thirds of the detemir group completed the study on twice daily detemir.<sup>6</sup>

In a 26 week study comparing twice daily detemir with once daily glargine as part of a basal bolus regimen in 320 subjects with type 1 diabetes, there was no difference in improvement in HbA1c at the end of the study. There was no difference in overall confirmed hypoglycaemia, however, severe and nocturnal hypoglycaemia were 72% and 32% lower, respectively, with detemir. There was no significant difference in body weight.<sup>7</sup>

In summary, basal insulin analogues appear to offer no clinically significant improvement in glycaemic control, but may offer reductions in severe and nocturnal hypoglycaemia. Insulin detemir may be associated with less weight gain than NPH insulin, but in many individuals will require twice daily dosing. It is important to interpret these findings in the context of cost; while an economic analysis of the benefits of basal insulin analogues in type 2 diabetes was undertaken, insufficient data were available in type 1 diabetes for a similar analysis, however both insulin glargine and insulin detemir cost more than NPH insulin.

### **Comparison of insulin detemir and insulin glargine: Children**

In both children and adolescents, compared with NHS insulins, neither of the basal insulin analogues, glargine nor detemir, was associated with a significant difference in HbA1c. No difference in hypoglycaemia was seen with glargine when compared with NPH insulin. In the one trial comparing detemir with NPH in pre-pubertal children and adolescents, no differences in severe hypoglycaemia were observed though there were minor reductions in nocturnal and overall hypoglycaemia.<sup>8</sup>

In children and adolescents, use of rapid-acting and basal insulin analogues offers at least similar glycaemic control, rates of overall hypoglycaemia, and rates of nocturnal hypoglycaemia to that of regular human insulin, and so both may be offered as alternatives.

## **Safety Summary**

The EPAR for insulin detemir (Levemir®)<sup>14</sup> states that, as part of the licensing process, a total 1248 subject years of exposure to insulin detemir were evaluated, 98% derived from the confirmatory intermediate and long-term trials. In total, 1732 subjects were exposed to insulin

detemir for 6 months or more.

The most common reported adverse events were upper respiratory tract infections, pharyngitis and headaches, diarrhoea and influenza-like symptoms for both the insulin detemir group and the NPH insulin group. The vast majority of AE's were classified as mild in severity. The only severe AE's reported in more than 1% of the subjects were hypoglycaemia-related events. The overall AE profile did not differ between insulin detemir and NPH insulin, except for injection site reactions. This AE was reported in 1.3% of the subjects treated with insulin detemir vs. 0.2% of the subjects treated with NPH insulin. Most of these reactions were mild, a few moderate, and no severe reactions were reported.

The only severe events reported in more than 1% of the subjects were coughing, myocardial infarction, cardiac failure and hypoglycaemic episodes. The overall AE profile in type 2 diabetes was comparable between the insulin detemir group and the NPH group. The only AE reported as more frequent in the NPH group was gastroenteritis.

### Cost Effectiveness Summary

SIGN 116 reports a UK health technology assessment of newer drugs for blood glucose control in type 2 diabetes, the incremental cost per quality adjusted life year (QALY) gained for use of glargine in place of NPH insulin was estimated at £320,029; for detemir the equivalent cost estimate was £417,625<sup>15</sup>

### Commissioning considerations:

### Comparative unit costs:

Drug	Presentation	Pack cost
Insulin detemir (Levemir®)	5x3 ml cartridge (100 units/ml solution)	£42.00
Insulin detemir (Levemir®)	5x3 ml pre-filled pen (100 units/ml solution)	£42.00
Insulin glargine (Lantus®)	5x3 ml cartridge (100 units/ml solution)	£41.50
Insulin glargine (Lantus®)	5x3 ml pre-filled pen (100 units/ml solution)	£41.50
Insulin degludec (Tresiba®)	5x3 ml cartridge (100 units/ml solution)	£72.00
Insulin degludec (Tresiba®)	5x3 ml pre-filled pen (100 units/ml solution)	£72.00 (£86.40 for 3x3 ml 200 units/ml solution)

Prices from April 2016 BNF, excluding VAT

## References

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- <sup>1</sup> Scottish Medicines Consortium advice 1126/16. March 2016 [https://www.scottishmedicines.org.uk/files/advice/insulin\\_detemir\\_Levemir\\_Abbreviated\\_FIN\\_AL\\_February\\_2016\\_for\\_website.pdf](https://www.scottishmedicines.org.uk/files/advice/insulin_detemir_Levemir_Abbreviated_FIN_AL_February_2016_for_website.pdf) [accessed online 27 April 2016]
  - <sup>2</sup> NICE Clinical Guideline 17: Type 1 diabetes in adults: diagnosis and management <https://www.nice.org.uk/guidance/ng17/resources/type-1-diabetes-in-adults-diagnosis-and-management-1837276469701> [accessed online 27 April 2016]
  - <sup>3</sup> NICE Clinical Guideline 28: Type 2 diabetes in adults: management <https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-1837338615493> [accessed online 27 April 2016]
  - <sup>4</sup> Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. *Diabet Med* 2008;25(4):442-9.
  - <sup>5</sup> Witthaus E, Stewart J, Bradley C. Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with Type 1 diabetes. *Diabet Med*. 2001;18(8):619-25
  - <sup>6</sup> Heller S, Koenen C, Bode B. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to target noninferiority trial. *Clin Ther*. 2009;31(10):2086-97
  - <sup>7</sup> Pieber TR, Treichel HC, Hompesch B, Philotheou A, Mordhorst L, Gall MA, et al. Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. *Diabet Med*. 2007;24(6):635-42. Epub 2007 Mar 22
  - <sup>8</sup> Robertson KJ, Schoenle E, Gucev Z, Mordhorst L, Gall MA, Ludvigsson J. Insulin detemir compared with NPH insulin in children and adolescents with Type 1 diabetes. *Diabet Med*. 2007;24(1):27-34
  - <sup>9</sup> Scottish Medicines Consortium advice 780/12. May 2012 [https://www.scottishmedicines.org.uk/SMC\\_Advice/Advice/780\\_12\\_insulin\\_detemir\\_Levemir\\_AB\\_BREVIATED/insulin\\_detemir\\_Levemir\\_ABBREVIATED](https://www.scottishmedicines.org.uk/SMC_Advice/Advice/780_12_insulin_detemir_Levemir_AB_BREVIATED/insulin_detemir_Levemir_ABBREVIATED) [accessed online 29 April 2016]
  - <sup>10</sup> NICE Clinical Guideline 18: Diabetes (type 1 and type 2) in children and young people: diagnosis and management <https://www.nice.org.uk/guidance/ng18/resources/diabetes-type-1-and-type-2-in-children-and-young-people-diagnosis-and-management-1837278149317> [accessed online 27 April 2016]
  - <sup>11</sup> SIGN Clinical Guideline 116: Management of diabetes <http://www.sign.ac.uk/pdf/sign116.pdf> [accessed online 27 April 2016]
  - <sup>12</sup> Canadian Agency for Drugs and Technologies in Health (CADTH). Long-Acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of Clinical Outcomes. Ottawa: CADTH; 2008. [cited 05 Jan 2010]. Available from url: [http://www.cadth.ca/media/compus/reports/compus\\_Long-Acting-Insulin-AnalogsReport\\_Clinical-Outcomes.pdf](http://www.cadth.ca/media/compus/reports/compus_Long-Acting-Insulin-AnalogsReport_Clinical-Outcomes.pdf) [accessed online 27 April 2016]
  - <sup>13</sup> Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues vs. NPH human insulin in type 1 diabetes. A metaanalysis. *Diabetes Obes Metab* 2009;11(4):372-8



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<sup>14</sup> EPAR for insulin detemir (Levemir®)

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR -  
Scientific Discussion/human/000528/WC500036658.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000528/WC500036658.pdf) [accessed online 27 April 2016]

<sup>15</sup> Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, et al. Newer agents for blood glucose control in type 2 diabetes. Health Technology Assess 2009; in press. Available from url: [http://www.journalslibrary.nihr.ac.uk/\\_data/assets/pdf\\_file/0009/65277/FullReport-hta14360.pdf](http://www.journalslibrary.nihr.ac.uk/_data/assets/pdf_file/0009/65277/FullReport-hta14360.pdf) [accessed online 27 April 2016]