



Therapeutic Class ReviewSM

Insulin detemir (Levemir[®])

February 2006

New Product(s) for Review

Insulin detemir (Levemir[®]) - Novo Nordisk

Dossier Provided by Manufacturer: yes

Available Therapeutic Alternatives

Insulins

Preferred/Formulary	Non-Prefer/Non-Formulary
<i>Rapid-Acting Insulin</i>	
insulin aspart: (Novolog [®]) [Novo Nordisk]	insulin glulisine: (Apidra [®]) [Sanofi Aventis]
insulin lispro: (Humalog [®]) [Eli Lilly]	
<i>Short-Acting Insulin</i>	
regular human insulin: (Humulin [®] R) [Eli Lilly]	
regular human insulin: (Novolin [®] R) [Novo Nordisk]	
<i>Intermediate/Long-Acting Insulin</i>	
isophane (NPH): (Humulin [®] N) [Eli Lilly]	
isophane (NPH): (Novolin [®] N) [Novo Nordisk]	
insulin glargine: (Lantus [®]) [Aventis]	insulin detemir: (Levemir) [Novo Nordisk]
<i>Pre-Mixed Insulin</i>	
lispro 75/25: (Humalog [®] Mix) [Eli Lilly]	
aspart 70/30: (NovoLog [®] Mix) [Novo Nordisk]	

Reason for Review

- Determine formulary/preferred status for insulin detemir (Levemir).
- Insulin detemir is a recently approved intermediate- to long-acting insulin analog with up to 24 hours duration of action.

Executive Summary

- Insulin detemir (Levemir) is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia.
- Structural differences from human insulin* and significant binding to albumin[‡] allow slower absorption from the injection site and prolonged release from albumin-binding sites.
- The FDA recognized open-label trials as sufficient to support approval for insulin detemir (Levemir). Factors they considered included:
 - Differences in product formulation which made blinding impractical. [Insulin detemir (Levemir) is a clear solution while NPH is cloudy]
 - Safety considerations due to pharmacodynamic differences.
- Endocrinologists indicate that insulin detemir (Levemir) offers little additional advantage over currently available intermediate to long-acting insulin products.

Evidence:

- Trials with insulin detemir (Levemir) compared to NPH or insulin glargine (Lantus) used an open label design, making it difficult to determine whether the results from the trials were due to the different insulin products or other unknown factors.
 - There is no useful evidence that insulin detemir (Levemir) provides a clinically relevant therapeutic advantage or disadvantage to insulin products currently available for use in either type 1 or type 2 diabetes.
 - There is no useful evidence that insulin detemir (Levemir) has a side-effect profile significantly different from comparable insulin products currently available for use in either type 1 or type 2 diabetes.
- Caution is urged regarding uncertain and/or not-useful evidence in making health care decisions.

Conclusion:

Insulin detemir (Levemir) is non-preferred/non-formulary because there is no useful evidence that insulin detemir (Levemir) provides additional clinical value over existing insulin products for the treatment/management of type-1 or type-2 diabetes.

[‡] More than 98% insulin detemir in the bloodstream is bound to albumin.

Products

Drug Product ^{1,2}	Date of FDA Approval ²	FDA Approved Indication(s)	Dose/Route	AWP Cost or MAC*	Potential Off-Label Use(s)
INSULIN				Cost of insulin per 10 mL vial	
regular human insulin: (Humulin [®] R)	10/1982	Diabetes mellitus – Type 1, Type 2, gestational, pregnancy, diabetic ketoacidosis, hyperglycemic-hyperosmolar nonketotic coma	Individualized per patient’s needs.	\$35	Diabetic ketoacidosis; hyperglycemic-hyperosmolar nonketotic coma
regular human insulin: (Novolin [®] R)	06/1991	Diabetes mellitus – Type I, Type 2, gestational, pregnancy, diabetic ketoacidosis, hyperglycemic-hyperosmolar nonketotic coma	Individualized per patient’s needs.	\$35	Diabetic ketoacidosis; hyperglycemic-hyperosmolar nonketotic coma
insulin aspart: (Novolog [®])	06/2000	Diabetes mellitus, Type 1 and Type 2	Individualized per patient’s needs.	\$81	
insulin lispro: (Humalog [®])	06/1996	Diabetes mellitus, Type 1 and Type 2	Individualized per patient’s needs.	\$81	
insulin glulisine (Apidra [®])	04/2004	Diabetes mellitus, Type 1 and Type 2	Individualized per patient’s needs.	\$81	
isophane (NPH): (Humulin [®] N)	10/1982	Diabetes mellitus – Type 1, Type 2, gestational, pregnancy, diabetic ketoacidosis, hyperglycemic-hyperosmolar nonketotic coma	Individualized per patient’s needs.	\$35	Hyperkalemia, diabetic neuropathy, diabetic macrovascular disease, latent autoimmune diabetes in adults, myocardial infarction
isophane (NPH): (Novolin [®] N)	07/1991	Diabetes mellitus – Type 1, Type 2, gestational, pregnancy, diabetic ketoacidosis, hyperglycemic-hyperosmolar nonketotic coma	Individualized per patient’s needs.	\$35	Hyperkalemia, diabetic neuropathy, diabetic macrovascular disease, latent autoimmune diabetes in adults, myocardial infarction
detemir : (Levemir [®]) ³	6/2005	Diabetes mellitus, Type 1 and Type 2	Individualized per patient’s needs.	Not yet established	
glargine: (Lantus [®])	04/2000	Diabetes mellitus Type 1 in adults and pediatric 6 yrs and older, Type 2 in adults	Individualized per patient’s needs.	\$91	
lispro 75/25: (Humalog [®] Mix)	12/1999	Diabetes mellitus, Type 1 and Type 2	Individualized per patient’s needs.	\$81	
aspart 70/30: (NovoLog [®] Mix)	11/2001	Diabetes mellitus, Type 1 and Type 2	Individualized per patient’s needs.	\$81	

*AWP (average wholesale price) based on First Data Bank as of January 2006 for 1 month of therapy.

References

1. Thomson Micromedex © 1974-2005. Micromedex Healthcare Series, Vol 120.
2. Center for Drug Evaluation and Research. Approval package for application number N021536. <http://www.fda.gov/cder/rdmt/nmecy2005.htm> (accessed November 10, 2005)
3. Levemir[®] (insulin detemir) Product Information. NovoNordisk Inc 2005. Accessed at <http://www.fda.gov/cder/foi/label/2005/0218781bl.pdf> . (accessed November 10, 2005)
4. Home P, Bartley P, Russell-Jones D, Hanaire-BROUTIN H, Heeg JE, Abrams P, et. al.; Study to Evaluate the Administration of Detemir Insulin Efficacy, Safety and Suitability (STEADINESS) Study Group. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes Care. 2004 May;27(5):1081-7.

5. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. *Clin Ther.* 2004 May;26(5):724-36.
6. Pieber TR, Draeger E, Kristensen A, Grill V. Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. *Diabet Med.* 2005 Jul;22(7):850-7.
7. Pieber TR, Treichel HC, Robertson LI, Mordhorst L, Gall M. Insulin detemir plus insulin aspart is associated with less risk of major as well as nocturnal hypoglycaemia than insulin glargine plus insulin aspart at comparable levels of glycaemic control in type 1 diabetes. *Diabetologia.* 2005; 47(Suppl 1): Abstract 242.
8. Hermansen K, Fontaine P, Kukulja KK, Peterkova V, Leth G, Gall MA. 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. *Diabetologia.* 2004 Apr;47(4):622-9.
9. Kolendorf K, Pavlic-renar I, Santeusanio F, Philotheou A, Gall M, Heller S. Insulin detemir is associated with lower risk of hypoglycemia compared to NPH insulin in people with type 1 diabetes. *Diabetes.* 2004; 53(Suppl. 2):A130
10. Robertson K, Schonle E, Gucev Z et al. Benefits of insulin detemir over NPH insulin in children and adolescents with type 1 diabetes: lower and more predictable fasting plasma glucose and lower risk of nocturnal hypoglycemia. *Diabetes.* 2004; 53(Suppl 2):A144
11. Haak T, Tiengo A, Draeger E, Suntum M, Waldhausl W. 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 Obes Metab.* 2005 Jan;7(1):56-64.
12. Hermansen K, Derezinski T, Kim H, Gall M. Treatment with insulin detemir in combination with oral agents is associated with less risk of hypoglycemia and less weight gain than NPH insulin at comparable levels of glycemic improvement in people with type 2 diabetes. *Diabetologia.* 2004; 47(Suppl 1):A273
13. Product Dossier: Levemir[®] (insulin detemir). Novo Study #1337 Novo Nordisk Inc., Princeton NJ. Data reviewed November 10, 2005.
14. Product Dossier: Levemir[®] (insulin detemir). Novo Study #1373 Novo Nordisk Inc., Princeton NJ. Data reviewed November 10, 2005.
15. Raslova K, Bogoev M, Raz I, Leth G, Gall MA, Hancu N. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract.* 2004 Nov;66(2):193-201.
16. American Diabetes Association: Standards of Medical Care in Diabetes. *Diabetes Care.* 2005;28:S4-S36. (assessed November 10, 2005)
17. American Diabetes Association Clinical Practice Recommendations. ADA Clinical Practice Guidelines. *Diabetes Care* 2004;27:S1-S142 (Supplement 1). http://care.diabetesjournals.org/content/vol27/suppl_1/
18. American Association of Clinical Endocrinologists Medical Guidelines for the Management of Diabetes Mellitus: the AACE System of Intensive Diabetes Self Management – 2002 Update. *Endocrine Practice* 2002 January/February; 8 (Suppl 1): 40-62 (assessed November 10, 2005)
19. De Leeuw I, Vague P, Selam JL, Skeie S, Lang H, Draeger E, 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 Obes Metab.* 2005 Jan;7(1):73-82.
20. Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. *Diabetes Technol Ther.* 2004 Oct;6(5):579-88.
21. Vague P, Selam JL, Skeie S, De Leeuw I, Elte JW, Haahr H, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care.* 2003 Mar;26(3):590-6.
22. Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. *Diabetes Care.* 2001 Feb;24(2):296-301
23. Roberts A, Bayer T, Munksgaard E, Lang H, Standl E. Efficacy and safety of 6-month treatment with insulin detemir in type 1 diabetic patients on a basal/bolus regimen. *Diabetes.* 2001; 50(Suppl. 2):A130.