Drug Use Research & Management Program
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Month/Year of Review: April 2012
PDL Class: DM - Insulin

Date of Last Review: September 2010
Source Document: Provider Synergies

Current Preferred Agents:

Short-Acting
Human insulin regular (Humulin® R)
Human insulin regular (Novolin® R)

Rapid-Acting
Insulin aspart (Novolog®)
Insulin lispro (Humalog®)

Rapid/Intermediate-Acting Combination
Insulin aspart 70/30 (Novolog® Mix)
Insulin lispro 50/50, 75/25 (Humalog® Mix)

Intermediate-Acting
Human insulin NPH (Humulin® N)
Human insulin NPH (Novolin® N)

Long-Acting
Insulin glargine (Lantus®)

Current Non-Preferred Agents:

Rapid-Acting
Insulin glulisine (Apidra® and Apidra Solostar®)

Long-Acting
Insulin detemir (Levemir®)

Previous Recommendations:

1. Evidence does not support a difference in efficacy/effectiveness
2. Evidence does not support a difference in harms or adverse events
3. Insulin aspart and lispro are both listed as Pregnancy Category B while insulin determir, glargine, and glulisine are listed as Pregnancy Category C
4. Recommend inclusion of at least one agent from each subgroup: Short acting, rapid acting, rapid/intermediate acting combination products, intermediate acting, long acting

PA Criteria/QL: Clinical criteria to approve insulin pens/cartridges. Requests for PA for school-aged children should be reviewed on a client specific basis.

Methods:

A MEDLINE OVID search was conducted using all included drugs in subjects with diabetes and limits for humans, English language, and controlled clinical trials or meta-analysis from September 2010 to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Trials:

A total of 318 citations resulted and after review for inclusions, five potentially relevant clinical trials were identified and brief details are described in table 1.

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results
Thalange , 2011[1] RCT, open-label	Detemir vs. NPH + insulin aspart with meals and snacks	Aged 2-16 yr with type 1 diabetes (n=348)	HbA1c at week 52	Mean HbA1c was similar between groups at baseline (8.2 vs. 8.1%), and changed little over 1 yr (8.1 vs. 8.3%).
Swinnen, 2010[2] Non-inferiority, open-label, RCT	Insulin glargine once daily vs. insulin detemir twice daily	Insulin-naïve type 2 diabetic patients on stable oral drugs, HbA1c 7.5-10% N=973	Percentage of patients reaching A1C <7% without symptomatic hypoglycemia @24 weeks	<u>% reaching A1C<%</u> Glargine: 27.5% Detemir: 25.6% difference: 1.85% [95% CI 3.78 to7.48%] *7 patients on glargine and 22 on detemir dropped out of the study due to adverse events (P < 0.005)
Fogelfeld, 2010[3] RCT, open-label, non-inferiority	Insulin lispro vs. insulin detemir	Insulin-naïve, type 2 diabetes, on ≥2 oral diabetic meds, HbA1c 7.5-10% N=442	Change from baseline in HbA1c (non-inferiority margin of 0.4%) @ week 24	<u>Change from baseline in HbA1c</u> Lispro: -1.47 ± 1.01% Detemir: -1.24 ± 1.11% LS difference: -0.21% [95% CI -0.39 to -0.03%]
Hsia, 2011[4] RCT, open-label	Bedtime NPH vs. bedtime glargine vs. morning glargine N=85	Adults with type 2 diabetes, HbA1c 7.5-12% despite treatment with oral medications, from inner city population	Between-group difference in the change of HbA1c from baseline.	<u>Change from baseline in HbA1c</u> NPH: -1.4 ± 1.7% Glar(PM): -1.3 ± 1.2% Glar (AM): -1.9 ± 1.4% differences between groups = -0.06%; 95% CI (-0.24 to 0.12), confirming noninferiority
Philotheou, 2011[5] RCT, open-label	Insulin glulisine vs. insulin lispro	4-17 years old, type 1 diabetes, HbA1c 6.0-11% (n=572)	Non-inferiority of glulisine to lispro in HbA1c at 26 week	<u>Change from baseline in HbA1c</u> Glulisine: +0.1 ± 0.08% Lispro: +0.16 ± 0.07% Glar (AM): -1.9 ± 1.4% • differences between groups = NS
HbA1c = hemoglobin A1c, NPH = neutral protamine Hagedorn, RCT = randomized controlled trial, NS = nonsignificant				

Systematic Reviews:

A Cochrane review from 2011 evaluated the comparative efficacy of insulin detemir and insulin glargine in the treatment of type 2 diabetes and identified four randomized trials directly comparing determir to glargine lasting 24 to 52 weeks. [6] Overall, risk of bias in the trials was high, mainly because all trials were open-label and neither participants nor study personnel were blinded. For the majority of efficacy outcomes, there was statistical heterogeneity between the studies. Overall, there was low quality evidence that there was no significant difference in efficacy in terms of change in HbA1c or hypoglycemic events. The mean difference in the endpoint of HBA1c between the agents was not statistically different (0.08%; 95% CI -.10 to 0.27). The percentage of patients achieving good glycemic control at study endpoint was similar between the two insulins (RR 0.96; 95%CI 0.81 to 1.14). There was also low quality evidence that there was no difference in safety between the two insulins. There was no difference in the relative risk of having at least once hypoglycemic event (RR 0.98; 95% CI 0.92 to 1.05), without evidence for statistically heterogeneity. There was high quality evidence that there was a difference in weight gain. Insulin detemir was associated with a statistically significant less weight gain than insulin glargine (mean difference of 0.91kg; 95% CI -1.21 to -0.61). There was insufficient evidence to make conclusions regarding quality of life, cost effectiveness, or mortality. To achieve the same glycemic control, it

was found that insulin detemir was often injected twice daily in a higher dose but with less weight gain, while insulin glargine was only injected once daily.

New drugs:
None

New FDA Indications:
In May 2011, the FDA approved insulin lispro (Humalog) use in a continuous insulin infusion pump in the pediatric population.

New FDA safety alerts:
None

Guidelines:
The American Association of Clinical Endocrinologists (AACE) 2011 Diabetes Care Plan Guidelines state that insulin is required in all patients with type 1 diabetes, and it should be considered for patients with type 2 diabetes, when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.[7] When insulin therapy is indicated in patients with type 2 diabetes, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and determir are preferred over intermediate-acting NPH because they are associated with less hypoglycemia. Short- or rapid-acting insulin may considered if postprandial hyperglycemia is present; rapid-acting insulin analogues being the prefer agent of the two because they have a more rapid onset and offset of action and are associated with less hypoglycemia. Premixed insulin analogue therapy may be appropriate for patients in whom adherence to a drug regimen is problematic; although, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared with basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.[7]

According to the AACE, the preferred treatment for postprandial hyperglycemia in pregnant women is regular or rapid-acting insulin analogues. Basal insulin can be controlled with the use of rapid-acting insulin via infusion pump therapy or long-acting insulin.[7]

Recommendations:

- No further research or review needed at this time.

References:

1. Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus. *Pediatr Diabetes*. 2011;12(7):632–641.

2. Swinnen SG, Dain M-P, Aronson R, et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. *Diabetes Care*. 2010;33(6):1176–1178.

3. Fogelfeld L, Dharmalingam M, Robling K, et al. A randomized, treat-to-target trial comparing insulin lispro protamine suspension and insulin detemir in insulin-naive patients with Type 2 diabetes. *Diabet. Med.* 2010;27(2):181–188.

4. Hsia SH. Insulin glargine compared to NPH among insulin-naïve, U.S. inner city, ethnic minority type 2 diabetic patients. *Diabetes Res. Clin. Pract.* 2011;91(3):293–299.

5. Philotheou A, Arslanian S, Blatniczky L, et al. Comparable efficacy and safety of insulin glulisine and insulin lispro when given as part of a Basal-bolus insulin regimen in a 26-week trial in pediatric patients with type 1 diabetes. *Diabetes Technol. Ther.* 2011;13(3):327–334.

6. Swinnen SG, Simon AC, Holleman F, Hoekstra JB, Devries JH. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2011;(7):CD006383.

7. Handelsman Y, Mechanick JI, Blonde L, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract*. 2011;17 Suppl 2:1–53.