



STATE MEDICAID P&T COMMITTEE MEETING  
 THURSDAY, October 16, 2008  
 7:00 a.m. to 8:30 a.m.  
 Cannon Health Building  
 Room 114



## MINUTES

**Committee Members Present:**

Kort DeLost, R.Ph.  
 Duane Parke, R.Ph.  
 Howard Weeks, M.D.

David Harris, M.D.  
 Matthew Rondina, M.D.

**Board Members Excused:**

Karen Gunning, Pharm D.  
 Raymond Ward, M.D.

Koby Taylor, Pharm D.  
 Jerome Wohleb, Pharm D.

**Dept. of Health/Div. of Health Care Financing Staff Present:**

Jennifer Zeleny, CPhT  
 Tim Morley, R.Ph.

Lisa Hulbert, R.Ph.

**University of Utah Drug Information Center Staff Present:**

John Vu, PharmD.

**Other Individuals Present:**

Craig Boody, Lilly	Mary Shefchyk, NNI	Dr. Forman, NNI
Amanda Walker, U of U	Melissa Archer, U of U	Ann Lingaard
Brett Brewer, EMD Serono	Lance Lindberg, U of U	Ben Focht, Amylin
Jay Jennings, Sanofi-Aventis	Donna Wahoff-Stice, UT Diabetes Center	

Meeting conducted by: Duane Parke, R. Ph.

1. Minutes for September 2008 were reviewed and approved.
2. DUR Board Update: There was no DUR Board update this month.
3. Long Acting Insulins and Insulin Mixtures: The first review will focus on insulin mixtures, also referred to as biphasic insulins. This refers to the insulins that contain a short-acting mealtime component along with a medium acting insulin portion for basal glucose control. For the numbers that are indicated with the insulin mixtures, the first number usually designates the amount of medium acting insulin and the second number usually designates the amount of short-acting component. There are 3 FDA approved biphasic human insulin products. These agents contain

Regular and a combination of NPH. There are Novolin 75/25, Humulin 70/30, and Humulin 50/50. Two lispro-based mixtures are available in the United States. They are Humalog 75/25 and 50/50 and there is one biphasic aspartate mix available, Novalog 70/30. There is also a recently approved Novalog 50/50 mix that was approved at the end of September; however, this product has not been marketed yet. There is no clinical data information published for this agent, and the company did not have any information available, so it is not included in the review.

For the review, the Drug Information Service conducted a Medline and Cochrane review. Initially they identified 266 titles. From this, 44 trials were retrieved for further review. A total of 8 trials were included in the review. The inclusion criteria were an A1C endpoint, at least 20 patients, there was a comparison between biphasic insulins, and the study was at least 12 weeks. There were no relevant Cochrane systematic reviews found. There was one AHRQ review on biphasic insulins that was done specifically in type 2 patients that was identified in the search. Only portions of this meta-analysis comparing the biphasic insulins to each other were included in this review. None of the trials reported morbidity as a primary outcome. Most studies compared an analog mix versus a regular mix. All of the data that are being included in this review are in patients with type 2 diabetes.

Two clinical questions were identified that were addressed in the review. The first is how does glycemic control compare between the biphasic insulins? This was answered in several parts. The first part is how aspartate 70/30 compares to human 70/30. There were 4 trials included in this section. All the trials did demonstrate an improvement in A1C from baseline, but there were no differences between groups. The AHRQ review did pool the results for these 4 trials and found no differences between the groups. For the biphasic insulin lispro versus human insulin 70/30, there were 3 trials. There was one trial comparing insulin lispro 75/25 with human insulin 70/30. No difference was detected between A1C levels after 3 months of treatment. There were 2 studies that looked at lispro 50/50 with human insulin 70/30. There were significant differences in A1C between the groups. The reduction with lispro was greater. These studies administered the biphasic insulins a little differently in the study, with one study administering the lispro 50/50 three times daily and the human 70/30 two times daily. The other study did not define a frequency of dosing for either group. The other comparison was between insulin lispro and insulin aspartate combinations. There were also no differences found between these two groups in the studies.

The second clinical question is how does the safety of the biphasic insulins compare with each other? With all of these insulins, hypoglycemia is the most serious adverse event reported. As far as differences in the rates of hypoglycemia, there was one trial included in which the rate of nocturnal hypoglycemia for the human insulin 70/30 per patient year was significantly greater compared to the aspartate 70/30. However, there were 2 trials that looked at the same comparison and did not find any significant difference between the groups. In conclusion, the biphasic insulins, in general, are equal to each other. There were two studies where insulin lispro 50/50 was possibly more effective than 70/30, but the dosing frequencies were either different or undefined in the trial. Also, the rates of hypoglycemia were generally similar between the biphasic insulins.

Dr. Barr Forman addressed the Committee. He is an endocrinologist and Medical Director with Novo Nordisk. Novo Nordisk had sent in the IMPROVE study that took patients who were on human 70/30 and converted them to Novolog 70/30. There was a 2.3% further reduction in A1C and over 90% less hypoglycemia. The problem with human insulins are those of the NPH, which is very

variable, and the delay in action of the regular. Analog mixtures are a better way to mimic mealtime insulin release. In that comparison, the analogs certainly have an advantage. As far as the 75/25, which is a Lilly product, most patients use a 70/30 mixture rather than the 75/25. The heat stability of the Novolog asparte may be an advantage over the other insulins. In general, mixture studies show that in patients with Type 2 diabetes, dosing once, twice, or three times a day provide further reductions of A1C. With one copay and one insulin, it makes it easier for patients to take. There is definitely a role of mixtures, and Novolog 70/30 has advantages.

Dr. Mahtab Sohrevardi, endocrinologist and Medical Director of the Diabetic Care Center addressed the Committee. She understands that there is a debate between Levemir and Lantus. In her personal experience, she does not see much of a difference either way. Possibly, the dose of Levemir might sometimes be higher, but there is no question about the consistency and the outcomes with Levemir. Some patients request Levemir because of the weight neutral effects of Levemir versus Lantus. A few studies show that, too.

John Vu addressed the Committee regarding long-acting insulins. What was included in this review was basically NPH, Detemir, and Galargine. NPH is often considered an intermediate insulin; however, it basically provides a basal type function like Lantus and Levemir, so it was included as a long acting insulin on this review. Lente and Ultralente are two other long acting insulins, but they are no longer available. Any studies that included them were not included. Pharmacodynamically, galargine generally has a 24 hour duration of action with no noticeable peak effect. NPH and detemir have a noticeable peak effect and are often dosed twice daily. A Medline and Cochrane search were conducted for this review. 158 titles were identified and a total of 17 randomized trials, one meta-analysis, and one Cochrane systematic review were included. There was one Cochrane review comparing detemir and galargine to NPH and lente in Type 1 diabetes. However, this was not included, since they pooled the NPH and lente group together, and lente is no longer available. Of all of the trials that were included, none of them assessed morbidity or mortality.

The first clinical question, how does glycemic control in Type 1 diabetes compare between the different long acting insulins? All but one trial compared a long acting insulin analog to NPH. There was one trial that did look at detemir versus galargine in Type 1 patients. With this study, there was no difference in A1C improvements. With the other studies, there were two comparative trials each looking at NPH versus galargine or NPH versus detemir that did find a difference in A1C. These trials showed that detemir and galargine improved A1C more than NPH in these trials. However, the differences between the two groups were for detemir versus NPH only 0.22% and for galargine versus NPH 0.2%. The clinical significance of these small differences may be questionable. In the remaining trials (6 comparing detemir to NPH and 3 comparing galargine to NPH), no significant differences in A1C were found. In Type 2 diabetes, there was one trial comparing detemir to galargine, and no significant differences were found between the two agents. For the remaining trials, there were 15 trials that had been included in either a meta-analysis or a Cochrane systematic review. In both the Cochrane and meta-analysis that were included, galargine was equally effective to NPH. In the meta-analysis there was a small but significant increase of 0.1% against the NPH, but this was not seen in the Cochrane review.

How does glycemic control compare between the different long-acting insulins when treating pediatric patients? There were two studies included in this review, one looking at detemir versus

NPH and one looking at galargine versus NPH. There were no significant differences in A1C reduction between the groups.

Looking at safety, the adverse events are generally similar to each other between the long acting products, except for hypoglycemia and weight gain. Rates of any hypoglycemia with NPH, including major or severe hypoglycemia and nocturnal hypoglycemia, were greater or equal to hypoglycemic rates observed with detemir or galargine in all trials. Hypoglycemic events were generally similar in studies that examined galargine and detemir. There were 2 studies that found a greater percentage of nocturnal hypoglycemia with galargine compared to detemir. There were no differences found between groups with the rates of any hypoglycemia or severe hypoglycemia in the same studies. Looking at body weight changes, body weight changes with both detemir and galargine were significantly lower than with NPH. In one of two studies comparing detemir and galargine, body weight was significantly greater with galargine compared with insulin detemir. Finally, looking at safety of pediatric patients, there was a single trial comparing detemir to NPH in pediatric patients, and a higher percentage of patients treated with NPH experienced a nocturnal hypoglycemic event. In a study comparing galargine to NPH, no significant differences were found in nocturnal hypoglycemic events. Both trials reported a similar percentage of patients experiencing severe or any hypoglycemic events.

In summary, the long acting insulins are effective for Type 1 and Type 2 diabetes. Insulin detemir and galargine are equally effective for A1C control based on the results of 2 head-to-head studies. Reductions in A1C with detemir and galargine were generally greater than or equal to the A1C reductions with NPH. The differences in adverse events between the long acting insulins included hypoglycemic rates and weight gain. Rates of hypoglycemia were generally lower with galargine and detemir than with NPH; however, this was not consistently seen in all trials. Body weight change for galargine and detemir were significantly lower or equal to changes seen with NPH.

Donna Wahoff-Stice, nurse practitioner, addressed the Committee. She currently works at the University of Utah in the Utah Diabetes Center. She is here to support maintaining Lantus on the PDL, and to give some background. Both her mother has diabetes, and her brother has Type 1. She has experience with diabetes both personally and as a practitioner. Her brother, when he changed from ultralente and NPH to Lantus, he said that it was smooth, that it changed his life, that he didn't have the peaks and valleys that he had before in his diabetes care. Looking even at the data that was presented today, there is no peak with Lantus as there is with detemir and NPH. She found in her clinical practice with her patients that there is peaking with detemir. Her patients have described Lantus as having changed their diabetes care. They feel more secure with their hypoglycemia. Another advantage of Lantus is that it is very easy to dose. She can give her patients minimal instructions with a little scale and they can titrate their own insulin based on their fasting blood sugar. This makes it easier on her and her patients to manage diabetes care. There is a study to back up a patient titrating their own insulin and being as effective as a clinician. Rarely does Lantus require two injections per day, so there is a decrease in cost and an increase in compliance associated with that. Her other experience with Levemir is that it does require a higher dosage. That was also mentioned by Dr. Sohrevardi. She had one patient that was switched from Lantus to detemir by a primary care doctor. She changed herself back to Lantus because she found that it cost her more money to have to buy an additional vial of detemir per month as compared to the Lantus. In summary, both of these insulins can be used to improve A1C. However, patients and her own

experience have been greater with Lantus. There is also an issue of requiring more of the detemir, which is a cost issue.

Dr. Forman stated that when a patient comes in, every patient is different. In order to get a true picture, it is necessary to look at larger studies. With individual patients, it is difficult to know whether an individual patient would have gained weight on insulin A versus insulin B. A practicing physician cannot say how a patient would have done on a particular insulin. To that point, the current issue of diabetes technology and therapeutics review by Davies showed that the weight gain was clearly greater with NPH and correlated with hypoglycemia, but not with detemir. There are real reasons, as yet unexplained, why there is less weight gain with detemir versus galargine or NPH. The 303 study showed that patients could titrate their own insulin and get better FBS and less hypoglycemia than if a doctor, nurse, or CDE directed them. The predictive study in Europe showed in a real experience where patients on oral agents or galargine or NPH and were switched to detemir, even in the group that was on galargine there was a further 0.5 reduction in A1C. The dose was at most 3-5% greater, but for that there was less hypoglycemia and weight loss. Part of the reason is that there is less hypoglycemia with detemir, so if there are less lows, the A1C goes up because there are less lows to negate the highs. That allows one to titrate up the detemir to further drop down the highs with less variability. An important point is that most studies do not show a significant difference in dosing. In individual patients, it can happen either way. The Committee is asked to consider data rather than personal experience in one or two patients. Important for cost is that once detemir is used, there is a 42 day half life. If a patient uses less than 1,000 units of detemir in 28 days, the detemir does not need to be refilled. This saves money and trips to the pharmacy. It is safe for use in geriatrics. The Garber review showed similar safety and efficacy in young people and older adults. A patient on Levemir with continuous glucose monitoring or Lantus and continuous glucose monitoring in the study presented at the ADA by King showed similar curves with same doses from one to the other. They are both good 24 hour insulins in Type 2. The problem is that this is a Danish company that wanted a multiple dose indication, so any study that is done in the United States could only use galargine by label once a day, but bid or once daily with Levemir. In the 303 study, 91% of the patients were on once daily detemir. The data supports 24 hour use, there is no sting when injected, and it is very efficacious. In non-inferiority studies, one will not see major differences in A1C, since the goal is to get a similar lowering of A1C.

Duane asked if all of the insulins are labeled for pediatrics. They are not labeled specifically for this indication.

The Committee felt that overall there is not enough clinically significant data. The nocturnal hypoglycemia that is shown with galargine versus detemir, but other than that there are no significant differences between them.

The Committee was concerned about the lack of data for especially the long acting insulins. The data is stronger in the mixed insulins, but there is not enough data for the long acting insulins. A physician may need to prescribe a different insulin based on individual patient characteristics. However, Duane pointed out that the PDL does offer physicians the opportunity to override.

Duane showed the Committee members the utilization data that was prepared for this meeting. Although utilization on the rapid acting analogs is spread fairly evenly, the long acting utilization

strongly favors Lantus. The Committee felt that the length of time that the Lantus has been on the market is probably the driving force behind this. Medicaid does take into account utilization when a preferred drug is selected.

The Committee asked Donna if there are differences in compliance among the long acting analogs. She sees compliance decrease with an increased number of injections per day. Once daily dosing is most often achieved with Lantus. Also, from a clinician's standpoint, the need to change the 80+% patients that are on Lantus to detemir and re-dose and re-titrate them would increase her work load and could potentially become a safety issue.

Dr. Forman stated that any time one changes a patient from one drug to another, there will be panicked patients. This has happened in his practice. Last time, with the rapid acting analogs, the choice was made that there should be at least two rapid acting analogs on the PDL. Looking at the utilization for the long-acting analogs, he would not want to switch the 80+% patients. New starts should have an equal choice. Probably both basal insulins should be on the list, because it is important for patients to have a choice and not everything works the same in all patients.

The Committee stated that having two potential choices would be valuable. The VA recognizes that even though the basal analogs most closely mimic normal insulin release, NPH is more cost-effective and effective in many patients in reducing their A1C to goal. The data does suggest that NPH is associated with a higher level of hypoglycemia, so for patients who are more brittle or difficult to control, that may be a less effective and potentially more dangerous option. If there will be two insulins on the PDL, NPH would still be a reasonable choice alongside either Lantus or Detemir.

Dr. Harris moved that there are no differences in safety or efficacy in the mixtures, and that at least one analog mixture plus one NPH mixture needs to be approved. Kort DeLost seconded the motion. The motion passed with votes by Kort DeLost, Dr. Rondina, Dr. Harris, and Duane Parke. Dr. Weeks voted against the motion.

Similarly, for long acting, there needs to be at least one analog and NPH included on the PDL. Kort DeLost seconded the motion. The motion passed with votes by Kort DeLost, Dr. Rondina, Dr. Harris, and Duane Parke. Dr. Weeks voted against the motion.

4. Business Update: This fiscal year, Medicaid has, to date, billed for \$862,000 and received so far \$416,000. Last year, which ended in June, Medicaid billed \$298,000 and received to date \$219,000. The rebate part of the PDL is working well, and Medicaid is pleased with the manufacturers for supporting the program. The other component of PDL cost savings is market shift. This can be just as great, or greater than the savings from supplemental rebates. Medicaid thanks the P&T Committee for their service to Medicaid and citizens of the state.

Next Meeting Set for Thursday, November 20, 2008  
Meeting Adjourned.

Minutes prepared by Jennifer Zeleny