New Drug Evaluation: Albiglutide

Month/Year of Review: January 2015
Generic Name: Albiglutide
PDL Class: Oral Hypoglycemics

End date of literature search: October 13, 2014
Brand Name (Manufacturer): Tanzeum™ (GlaxoSmithKline)
Dossier Received: Yes

FDA Approved Indication:¹

Albiglutide is a subcutaneous (SC) glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Albiglutide is not recommended as first-line therapy for patients unable to control glucose levels with diet and exercise and should not be given to patients with type 1 diabetes.

Research Questions:
- Is there evidence of superior efficacy of albiglutide compared to other T2DM therapies when considering important outcomes such as hemoglobin A1c (HbA1c) lowering and reduced microvascular and macrovascular outcomes?
- Is there evidence albiglutide has a better safety profile than other treatments for T2DM?
- Are there subgroups of patients which albiglutide shows improved efficacy or greater risk of harms?

Conclusions:
- There is insufficient evidence at this time that albiglutide reduces microvascular or macrovascular outcomes.
- There is moderate strength of evidence that albiglutide 30 mg weekly is effective in lowering HbA1c by -0.55% to -0.89% when used in combination with other treatments.²⁻⁷ Published trials showed albiglutide to be superior to sitagliptin (2 studies),³⁷ glimepiride (1 study)³ and placebo (2 studies).³⁻⁵ Open-label comparison trials found albiglutide to be non-inferior to insulin glargine and insulin lispro.⁴⁻⁵ Albiglutide was found to be inferior to liraglutide (open-label study) and pioglitazone (unpublished study).⁶
- Efficacy of albiglutide is limited by the potential for performance and assessment bias due to open-label study designs and insufficient information on study design and methodology.
- The most common adverse effects seen with albiglutide are gastrointestinal and injection site reactions. The incidence of injection site reactions was higher with albiglutide compared to other injectable products; comparisons of albiglutide to daily GLP-1 agonist, liraglutide, resulted in a number-needed-to-harm (NNH) of 13. Withdrawals due to adverse reactions were higher with albiglutide, most commonly due to nausea and injection site reactions.¹⁻⁷
Weight loss (-0.64 to -1.21 kg), low risk of hypoglycemia and once weekly dosing are may be advantages of albiglutide treatment compared to other therapies in some patients.¹⁻⁷

Recommendations:

- Recommend adding albiglutide to the current prior authorization criteria for GLP-1 receptor agonists (Appendix 1). Recommend limiting use of albiglutide to patients that have tried and failed other treatments for T2DM. No changes to the PDL are recommended.

Reason for Review:

Albiglutide is once weekly GLP-1 receptor agonists for the treatment of T2DM. Comparison of the efficacy and safety data of albiglutide to other T2DM treatments is necessary for the management of the preferred drug list (PDL) and prior authorization (PA) criteria.

Background:

Type 2 diabetes mellitus is a prevalent disease which affects an estimated 25.6 million people in the United States.⁸ Despite a variety of treatments, a significant number of patients fail to meet A1C goals and within three years of being diagnosed 50% of patients require combination therapy to control rising glucose levels. According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2DM by 2050.⁹ Treatment guidelines recommend a trial of lifestyle modifications to control hyperglycemia in patients with T2DM and add pharmacotherapy for persistent elevated glucose levels. Guidelines recommend a goal HbA1C of less than 7% to minimize macrovascular and microvascular complications. Lower or higher HbA1c goals may be appropriate depending on patient specific characteristics. Therapy should be tailored according to patient factors, such as concomitant comorbidities.¹⁰,¹¹ A number of therapeutic options are available for management of glycemic variances associated with T2DM.¹² Classes of anti-hyperglycemic agents (AHA) currently available are: alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, sodium-glucose co-transporter 2 (SGLT2) inhibitors, insulins, meglitinides, sulfonylureas, thiazolidinediones (TZD), bile acid sequestrants, dopamine-2 agonists and amylin mimetics.

Important outcomes in patients with diabetes are: mortality, microvascular complications (chronic kidney disease, retinopathy, peripheral neuropathy) and macrovascular complications (cardiovascular events, stroke/ischemic attacks, coronary heart disease, amputations). Intermediate outcomes of interest are Hba1C and weight. Adverse event outcomes are: severe adverse events, hypoglycemia rates, and withdrawals due to adverse events. Hemoglobin A1C is often used as a surrogate outcome to assess comparative efficacy of different AHA therapies, as hyperglycemia has been shown to correlate with microvascular complications and potentially macrovascular outcomes.¹¹ Available data are limited to short-term studies, which prevents the assessment of the durability of available AHAs to control glucose levels long-term and to compare the effectiveness of AHAs on outcomes such as microvascular and macrovascular complications. Differing definitions of hypoglycemia also complicate the comparisons of safety between the differing AHA agents. Available evidence suggests that metformin is likely to reduce the incidence of cardiovascular disease based on data from the United Kingdom Prospective Diabetes Study (UKPDS) trial.¹¹ UKPDS data has also indicated a reduced incidence of microvascular risk with sulfonylureas and insulin therapy. Thiazolidinediones, alpha-glucosidase inhibitors and dopamine-2 agonists have studies that suggest reduced cardiovascular disease events but additional data are needed.¹¹ The effects of many of the AHAs on long-term complications of T2DM remain unknown.

Clinical Efficacy:

Albiglutide was studied in six, phase 3 trials in nearly 4,000 patients.²⁻⁷ Study design, inclusion and exclusion criteria and primary endpoints were similar for all studies. Trials included adult patients (mean age of 56 years) with baseline HbA1c between 7% and 10.55 with normal renal function (creatinine clearance >60

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mL/min), with the exception of one study in patients with reduced renal function (HARMONY 7). All trials included the comparison of 30 and 50 mg weekly doses of subcutaneous (SC) albiglutide, except for HARMONY 1, which only studied the 30 mg dose. Patients were allowed to receive rescue therapy for hyperglycemic rescue if pre-defined FPG and HbA1c values were met. The primary outcome measure was change in HbA1c from baseline. Trial durations lasted 8 months to 3 years. Secondary endpoints included decreases in fasting blood glucose (FPG), number of patients obtaining an HbA1c less than 7%, change in weight and number of patients requiring rescue therapy for hyperglycemia.

HARMONY 1
In a fair-good quality trial, 310 patients were randomized to albiglutide 30 mg weekly to placebo in patients taking background pioglitazone with or without metformin, representing 80% of patients. Mean patient age was 55 years and mean HbA1c was 8.1%. Patients with obesity were largely included with a mean patient BMI of 34 kg/m². Results at 52 weeks showed albiglutide lowered HbA1c more than placebo (-0.8% vs. -0.1%, respectively; mean difference -0.7% [95% confidence interval (CI) -1.0 to -0.6, p<0.0001]). The number or patients obtaining an HbA1c less than 7% was significantly greater in the albiglutide group with a number needed to treat (NNT) of 3 versus placebo.

HARMONY 3
In a poor-fair quality trial, 999 were randomized to albiglutide 30 mg weekly, sitagliptin 100 mg orally daily, glimepiride 2 mg daily or placebo. Doses of albiglutide could be increased to 50 mg weekly and the dose of glimepiride could be increased to 4 mg daily if predetermined elevated glucose levels were met. Enrolled patients were subject to at 4-week run-in and stabilization period. Patients were allowed to be on concomitant metformin. Overall attrition rates were high with less than 70% completing the study. Mean change in HbA1c at 104 weeks was significantly better for albiglutide compared to sitagliptin, glimepiride, and placebo with HbA1c lowering of -0.63%, versus -0.28%, -0.36% and 0.27%, respectively. More patients in the albiglutide group obtained an HbA1c goal of less than 7% and less patients in the albiglutide group required hyperglycemic rescue when compared to sitagliptin, glimepiride and placebo.

HARMONY 4
In this non-inferiority study, albiglutide 30 mg weekly was compared to insulin glargine 10 units SC daily in 735 patients. HARMONY 4 was an open-label study that allowed for an increase treatment doses of up to 50 mg weekly in the albiglutide arm and increases in insulin glargine arm based on weekly self-monitored blood glucose levels. In this fair quality study, patients were allowed to continue metformin with or without sulfonylurea therapy. Albiglutide was non-inferior to insulin glargine at lowering HbA1c at week 52 (insulin glargine -0.79% vs. albiglutide -0.67%). Hyperglycemia rescue was higher in the albiglutide group; however, weight loss was significantly more in the albiglutide group.

HARMONY 6
In this poor-fair quality, open-label, non-inferiority trial, albiglutide 30 mg weekly was compared to insulin lispro given SC three times daily with meals in patients currently receiving insulin glargine. All patients also received concomitant metformin and pioglitazone. Insulin glargine and insulin lispro doses were titrated based on glucose levels and the albiglutide dose could be increased to 50 mg weekly if indicated. The study comprised of 563 moderately uncontrolled patients with T2DM with a mean baseline Hba1c of 8.45%. At week 26, albiglutide was non-inferior to insulin lispro at lowering HbA1c (albiglutide -0.82% vs. insulin lispro -0.66%). Weight changes were minimal in both groups though considered statistically significant by study investigators (albiglutide -0.7 kg vs. insulin lispro +0.8 kg).

HARMONY 7
Author: Kathy Sentena, Pharm.D.
In this fair quality, open label, non-inferiority trial, 805 patients were treated with either albiglutide 30 mg weekly, titrated to 50 mg at 6 weeks, or liraglutide 0.6 mg SC daily (titrated to 1.2 mg at week 1 and 1.8 mg at week 2) with changes in HbA1c documented at 32 weeks. Almost all patients were on concomitant oral treatment for diabetes, most commonly a sulfonylurea and metformin. At week 32, HbA1c lowering was greater in the liraglutide group (-0.99%) compared to albiglutide (-0.78%) and non-inferiority was not met. Injection site reactions were more common in the albiglutide group. Gastrointestinal events were higher in liraglutide patients.

HARMONY 8

Albiglutide was studied in patients with mild, moderate and severe renal impairment in a fair-good quality trial involving 495 patients (HARMONY 8). Patients received albiglutide 30 mg weekly, titrated to 50 mg if indicated, compared to sitagliptin dosed based on renal function outlined in the prescribing information. Ninety-three percent of patients had mild to moderate renal dysfunction. Patients were allowed to continue metformin, pioglitazone and sulfonylureas. At week 26, albiglutide was superior to sitagliptin with a difference in HbA1c -0.32% (95% CI -0.49 to -0.15, p=0.0003 for superiority). The number of patients meeting an HbA1c goal of less than 7% was higher in the albiglutide group, with a NNT of 8. Significantly less patients in the albiglutide group received treatment for hyperglycemic rescue.

In an unpublished study, albiglutide 30 mg weekly was not non-inferior to pioglitazone 30 mg daily in 657 patients with T2DM who were not controlled on metformin (≥1500 mg/day) and glimepiride (4 mg/day). Baseline characteristics were similar to other trials. The non-inferiority margin of 0.3% against pioglitazone was not met. Changes in HbA1c were highest for pioglitazone (-0.8%), followed by albiglutide (-0.6%) and an increase in the placebo group (0.3%).

Phase 3 studies of albiglutide ranged from poor-fair to good quality. Open-label study design used in three trials allows for a high chance for performance bias. Screening and run-in periods allow for exclusion of patients not able to tolerate medications, which decreased applicability of these results. In trials with insulin comparative groups, titration was not always maximized or done in a systematic fashion, which may have allowed for sub-optimal comparative treatment and reduced glucose control in insulin treated groups.

Clinical Safety

The most common adverse reactions reported in greater than 10% of patients were upper respiratory infections, diarrhea, nausea and injection site reactions. In placebo-controlled trials, nausea occurred in 9.6% of patients taking placebo compared to 11.1% in those taking albiglutide. Injection site reactions in a pooled analysis of placebo-controlled trials occurred at a rate of 8% for the placebo group and 18% for albiglutide patients. Results were similar in a pooled analysis of placebo and active treatment trials, with the exception of hypoglycemia. Symptomatic hypoglycemia rates were similar with albiglutide and placebo, 2% in each group, and more common than placebo when albiglutide was combined with insulin or a sulfonylurea. Most common reasons for study withdrawals due to adverse events were due to nausea and injection site reactions.

Severe adverse reactions more common with albiglutide than placebo and active controls were pneumonia and appendicitis. Acute pancreatitis has also been reported with albiglutide. Data from eight clinical trials demonstrated an increased risk of pancreatitis with albiglutide than those receiving placebo or active treatment comparisons, at an incidence of 0.3%, 0% and 0.1%, respectively. Anti-albiglutide antibodies were noted in 116 (5.5%) patients taking albiglutide in a pooled analysis of seven trials though it is unknown if these will alter the effectiveness of albiglutide in real world situations. Albiglutide was not associated with an increased risk in cardiovascular events.

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Conclusion:
In conclusion, there is moderate strength of evidence that albiglutide lowers HbA1c by -0.55% to -0.89% when used in combination with other treatments. Small decreases in weight and low incidences of hypoglycemia are benefits of treatment. Common adverse reactions include gastrointestinal issues and injection site reactions. Ongoing monitoring of risk of pancreatitis and thyroid cancers will important as albiglutide is used long-term.
### COMPARATIVE CLINICAL EFFICACY

**Relevant Endpoints:**
1. Microvascular outcomes
2. Macrovascular outcomes
3. Goal HbA1c
4. Hypoglycemia
5. Quality of life
6. Serious adverse reactions
7. Changes in weight

#### Primary Study Endpoint:
1) Change in HbA1c from baseline

#### Relevant Endpoints:

<table>
<thead>
<tr>
<th>Ref./Study Design</th>
<th>Drug Regimens/ Duration</th>
<th>Patient Population</th>
<th>Outcomes/Efficacy Results (98.5% CI, p-values)</th>
<th>Arr/ NNT</th>
<th>Safety Results (CI, p-values)</th>
<th>Arr/ NNH</th>
<th>Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns</th>
</tr>
</thead>
</table>
| Reusch, et al 2014 (HARMONY-1) | 1. Albiglutide 30 mg SC weekly (A) 2. Placebo SC weekly (P) | *Patients were on background pioglitazone and metformin* | **Demographics:**  
   - Age (mean): 55 years  
   - Female: 40%  
   - Baseline HbA1c (mean): 8.1%  
   - BMI (mean): 34.1 kg/m²  
| **Inclusion Criteria:**  
   - Patients ≥18 years old, body mass index of 20-45 kg/m², non-pregnant and non-lactating, HbA1c of 7-10% with type 2 diabetes and on stable doses of pioglitazone, with or without metformin for at least 2 months before randomization.  
| **Exclusion Criteria:**  
   - History of active cancer, diabetic gastroparesis, biliary disease, pancreatitis, significant cardiovascular or cerebrovascular diseases, HIV, GI surgery, family history of | **Primary Endpoint**  
   - Change in HbA1c at 52 weeks (model-adjusted):  
   - A: -0.8%  
   - P: -0.1%  
   - Treatment difference:  
     -0.8% (95% CI: -1.0 to -0.6, p<0.0001 for superiority)  
| **Secondary Endpoints**  
   - Patients Obtaining HbA1c <7%:  
   - A: 66 (44.3%)  
   - P: 22 (14.8%)  
   - P<0.0001  
| **Changes in Weight at week 52:**  
   - A: 0.28 kg  
   - P: 0.45 kg  
| **Discontinuations due to Adverse Events:**  
   - A: 7 (4.7%)  
   - P: 10 (6.6%)  
   - p-value not reported  
| **Symptomatic Hypoglycemia:**  
   - A: 5 (3.3%)  
   - P: 2 (1.3%)  
   - p-value not reported  
| **Nausea:**  
   - A: 16 (10.7%)  
   - P: 17 (11.3%)  
   - p-value not reported  
| **Injection site reactions:**  
   - A: 17 (11.3%)  
   - P: 17 (7.9%)  
   - p-value not reported  
| **Quality rating:** Fair - Good  
| **Internal Validity:**  
   - **Selection:** Randomized; interactive voice response system based on sequestered fixed randomization schedule.  
   - **Performance:** Patients and caregivers blinded and efforts made to conceal treatment allocation.  
   - **Detection:** No details provided.  
   - **Attrition:** High overall attrition; ITT analysis with LOCF  
| **External Validity:**  
   - **Recruitment:** Patients from 158 centers and 4 countries were included.  
   - **Patient Characteristics:** Majority of patients (80%) on concomitant pioglitazone and metformin. Baseline HbA1c indicates patients only moderately uncontrolled.  
   - **Outcomes:** Accepted surrogate end-point used. Data on long-term health outcomes are lacking.  

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<tr>
<th>Study ID</th>
<th>Drug/Placebo</th>
<th>Dose</th>
<th>Demographics</th>
<th>Primary Endpoint</th>
<th>Discontinuations due to Adverse Events</th>
<th>Quality rating</th>
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</thead>
<tbody>
<tr>
<td>Ahrén et al 2014</td>
<td>Albiglutide 30 mg SC weekly (A)*</td>
<td>1.0</td>
<td>Demographics: Age (mean): 55 years Male: 48% Baseline HbA1c (mean): 8.1% BMI (mean): 32.8 kg/m² Inclusion Criteria: Patients ≥18 years old, body mass index of 20-45 kg/m², creatinine clearance &gt;60 mL/min, normal thyroid function, not clinically euthyroid, HbA1c of 7-10% with T2DM and experiencing inadequate glycemic control despite metformin for ≥3 months before screening. Exclusion Criteria: History of active cancer, gout, inflammatory disease, pancreatitis, significant cardiovascular or cerebrovascular diseases, HIV, GI surgery, family history of medullary carcinoma or multiple endocrine neoplasia type 2, resting systolic blood pressure &gt;160 mmHg and/or diastolic blood pressure &gt;100 mmHg or abnormal lab values.</td>
<td>Primary Endpoint Change in HbA1c at 104 weeks: A: -0.63% S: -0.28% G: -0.36% P: 0.27% Mean Treatment Difference: A: -0.9% S: -0.4% G: -0.3% P: -0.1% A vs. S: p=0.0001 A vs. G: p=0.0033 A vs. P: p&lt;0.0001 Secondary Endpoints: Patients Obtaining HbA1c &lt;7%: A: 113 (38.6%) S: 94 (31.6%) G: 94 (31.4%) P: 15 (15.5%) A vs P, S vs P, G vs P: p&lt;0.0001 Change in Weight at Week 104: A: -1.21 kg S: -0.86 kg G: 1.17 kg P: -1.0 kg p-value not reported</td>
<td>Discontinuations due to Adverse Events: A: 20 (6.6%) S: 11 (3.6%) G: 14 (4.6%) P: 5 (5%) p-value not reported</td>
<td>Internal Validity: Selection: No details provided. Performance: Patients and caregivers blinded. Matching placebos for albiglutide, sitagliptin, and glimepiride were used to maintain blinding. Detection: No details provided. Attrition: High overall attrition; ITT analysis with LOCF. External Validity: Recruitment: Patients from 289 centers and 10 countries included. Patient Characteristics: Moderately to severely obese patients accounted for 67% of study participants. Run-in/stabilization phase of 4 weeks could eliminate patients unable to tolerate medication before start of trial. Patients randomized to albiglutide on mean dose of 40.5 mg weekly and those on glimepiride on mean dose of 3.1 mg daily. Outcomes: Accepted surrogate end-point used. Data on long-term health outcomes are lacking</td>
</tr>
</tbody>
</table>

| Weissman et al 2014 | Albiglutide 30 mg SC daily (A) | 1.0 | Demographics: Age (mean): 49 years Male: 55% Baseline HbA1c (mean): 8.1% BMI (mean): 32.8 kg/m² Inclusion Criteria: Patients ≥18 years old, body mass index of 20-45 kg/m², creatinine clearance >60 mL/min, normal thyroid function, not clinically euthyroid, HbA1c of 7-10% with T2DM and experiencing inadequate glycemic control despite metformin for ≥3 months before screening. Exclusion Criteria: History of active cancer, gout, inflammatory disease, pancreatitis, significant cardiovascular or cerebrovascular diseases, HIV, GI surgery, family history of medullary carcinoma or multiple endocrine neoplasia type 2, resting systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg or abnormal lab values. | Primary Endpoint Change in HbA1c at 104 weeks: A: -0.63% S: -0.28% G: -0.36% P: 0.27% Mean Treatment Difference: A: -0.9% S: -0.4% G: -0.3% P: -0.1% A vs. S: p=0.0001 A vs. G: p=0.0033 A vs. P: p<0.0001 Secondary Endpoints: Patients Obtaining HbA1c <7%: A: 113 (38.6%) S: 94 (31.6%) G: 94 (31.4%) P: 15 (15.5%) A vs P, S vs P, G vs P: p<0.0001 Change in Weight at Week 104: A: -1.21 kg S: -0.86 kg G: 1.17 kg P: -1.0 kg p-value not reported | Discontinuations due to Adverse Events: A: 20 (6.6%) S: 11 (3.6%) G: 14 (4.6%) P: 5 (5%) p-value not reported | Quality rating: Poor - Fair |

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Attrition</th>
<th>Change in HbA1c from baseline at 52 weeks</th>
<th>Change in Weight at week 52</th>
<th>Adverse Events</th>
<th>Symptomatic Hypoglycemia</th>
<th>Nausea</th>
<th>Injection site reactions</th>
<th>Discontinuations due to Adverse Events</th>
<th>Quality rating</th>
</tr>
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<tbody>
<tr>
<td>2014 (HARMONY 4) OL, PG, NI, RCT 222 Centers in 4 countries</td>
<td>randomized 2014</td>
<td>2. Insulin glargine SC 10 units daily** (G)  • Patients on metformin with or without a sulfonylurea  • Study duration is 3 years with results reported at 1 year.  • 4 weeks of placebo run-in  * Dose could be increased to 50 mg weekly.  **Dose could be increased weekly based on SMBGs.</td>
<td>Attrition: 22% G: 239 (200) Attrition: 16%</td>
<td>Change in HbA1c from baseline at 52 weeks: A: -0.67% G: -0.79% Treatment difference: 0.11% (95% CI -0.4 to 0.27, p=0.0086 for non-inferiority)</td>
<td>Change in Weight at week 52: A: -1.06 kg G: 1.57 kg Mean difference: -2.61 kg (95% CI -3.20 to -2.02 P&lt;0.0001)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Poor to Fair</td>
</tr>
<tr>
<td>Rosenstock, et al 2014 (HARMONY 6) OL, NI, Phase 3, PG, RCT</td>
<td>randomized 2014</td>
<td>1. Albiglutide 30 mg SC once weekly* (A) + insulin glargine SC daily  2. Insulin lispro SC TID with meals (L) + insulin glargine SC daily  • Background metformin and/or pioglitazone allowed</td>
<td>Demographics: Age (mean): 56 years Male: 47% Baseline HbA1c (mean): 8.45% Weight (mean): 92 kg</td>
<td>Primary Endpoint Change in HbA1c from baseline at 26 weeks: A: -0.82% L: -0.66% Treatment difference: -0.16% (95% CI -0.32 to 0.00, p&lt;0.0001 for non-</td>
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<tr>
<th>Pratley R, et al 20146 (HARMONY 7) OL, NI, Phase 3, PG, RCT 162 Centers and 8 Countries</th>
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<tbody>
<tr>
<td><strong>Demographics:</strong> Age (mean): 55 years Male: 50% Baseline HbA1c (mean): 8.16% BMI (mean): 32.8 kg/m²</td>
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<tr>
<td><strong>Primary Endpoint</strong> Change in HbA1c from baseline at 32 weeks: A: -0.78% L: -0.99% Treatment difference: 0.21% (95% CI 0.08 to 0.34, p=0.0846 for non-inferiority)</td>
</tr>
<tr>
<td>Secondary Endpoints Patients Obtaining HbA1c &lt;7%: A: 168 (42%) L: 208 (52%) P=0.0023</td>
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<tr>
<td>Injection site reactions: A: 28 (12.9%) L: 5 (5.4%) P=0.0002</td>
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</table>

**Recruitment:** Not described.

**Patient Characteristics:**
- Baseline HbA1c 8.5%, indicates only moderately uncontrolled patients included.
- Significantly younger patient age in albiglutide group.
- Almost 70% of patients in both groups on concomitant metformin and 23.5% on neither metformin nor TZD.
- GLargines doses increased at similar rates in albiglutide and lispro arms.
- Lispro dose increased from baseline 15.5 IU to 30.6 IU.
- In albiglutide arm 51% of patients increased dose to 50 mg before week 26.

**Outcomes:** Accepted surrogate end-point used. Data on long-term health outcomes are lacking.

**Quality rating:** Fair

**Internal Validity:**
- **Selection:** Patients were randomized via an independent randomization schedule done by an independent randomization team. Assignments were done by an interactive voice recognition system.
- **Performance:** Open-label subject to a high degree of bias.
- **Detection:** No details were provided.
- **Attrition:** Attrition was 14% in the albiglutide group and 16% in the liraglutide group; mITT analysis done with LOCF.

**External Validity:**
- **Recruitment:** Patients from 162 centers and 8 countries. Six
Leiter L, et al 2014 (HARMONY 8)
DB, Phase 3, PG RCT
134 Centers and 15 Countries

1. Albiglutide 30 mg SC once weekly* (A)
2. Sitagliptin 25-100 mg PO daily**
   - 52 week treatment duration with 2 week screening and 4 week run-in
   - Mild renal impairment (eGFR ≥60 to ≤89 mL/min/1.73 m²)
   - Moderate renal impairment (eGFR ≥30 to ≤59 mL/min/1.73 m²)
   - Severe renal impairment ≥15 to ≤29 mL/min/1.73 m²
   - Patients allowed to take metformin, TZDs, or sulfonylureas
   - If GFR fell below 60 mL/min/1.73 m² patients were titrated off metformin
   *titrated to 50 mg if needed.
   **Renal dosing per recommendations in

<table>
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<tr>
<th>Demographics:</th>
<th>A: 249 (198) Attrition: 21%</th>
<th>Primary Endpoint</th>
<th>Discontinuations due to Adverse Events:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean): 63.3 years Male: 54% Baseline HbA1c (mean): 8.2% BMI (mean): 30.4 kg/m²</td>
<td>A: -0.64 kg L: -2.19 kg P&lt;0.0001</td>
<td>at 32 weeks:</td>
<td>A: -0.83% S: -0.52% Treatment difference: -0.32% (95% CI -0.49 to -0.15, p=0.0003 for superiority)</td>
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<tr>
<td>Inclusion Criteria: Patients 18 years or older with T2DM, renal impairment (mild, moderate or severe), inadequately controlled on glargine, detemir, or NPH insulin, with or without oral antihyperglycemic drugs for ≥6 months and ≤4 years; HbA1c 7.0-10.0%, BMI ≥20 kg/m² and ≤45 kg/m², fasting C-peptide level of ≥0.8 ng/mL, GFR of ≥15 to &lt;90 mL/min/1.73 m², hemoglobin of ≥11 g/dL for male patients and ≥10 g/dL for female patients.</td>
<td>S: 246 (178) Attrition: 28%</td>
<td>S: 26 (10.6%) p-value not reported</td>
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</tr>
<tr>
<td>Exclusion Criteria: Malignancy, history of diabetic gastroparesis, ongoing symptomatic biliary disease, history of pancreatitis, significant gastrointestinal surgery, HIV, Hepatitis B or C,</td>
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<td>Symptomatic Hypoglycemia:</td>
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<td>A: 29 (11.6)% S: 15 (6.1%) p-value not reported</td>
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<td></td>
<td></td>
<td></td>
<td>Nausea:</td>
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<td></td>
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<td>A: 12.8 (4.8%) L: 8 (3.3%) p-value not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Injection site reactions:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A: 20 (8.0%) S: 9 (3.7%) p-value not reported</td>
</tr>
</tbody>
</table>

Quality rating: Fair - Good

Internal Validity:
Selection: Patients were randomized via an interactive voice response system.
Performance: Described as double blind and efforts were made to conceal treatment allocation.
Detection: No details provided.
Attrition: Moderate-high attrition in both groups; ITT analysis done.

External Validity:
Recruitment: Patients from 134 centers and 15 countries.
Patient Characteristics:
- The mean baseline HbA1c was 8.2%, indicating that there were only moderately uncontrolled.
- Patients with mild renal impairment accounted for 52%, moderate renal impairment 41% and severe renal impairment 7% of study participants.
- The mean albiglutide dose was 40.2 mg.
Outcomes: Accepted surrogate end-point used. Data on long-term health outcomes are lacking.

Author: Kathy Sentena, Pharm.D.
| prescribing information | abnormal lab values, significant cardiovascular or cerebrovascular disease, pregnancy or lactation. |


References:


Author: Kathy Sentena, Pharm.D.
Appendix 1: Current PA Criteria and Proposed Changes

Incretin Mimetics (GLP-1 Analogs)

Initiative: To optimize the correct use of insulin mimetics.

Length of Authorization: Up to 1 year

Preferred Alternatives:
- Non-preferred drugs

Covered Alternatives:
- Preferred alternatives listed at [www.orpdl.org](http://www.orpdl.org)

<table>
<thead>
<tr>
<th>Approval Criteria</th>
<th>Yes: Go to #2</th>
<th>No: Pass to RPH; Deny for medical appropriateness.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the patient have a diagnosis of Type 2 diabetes?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Will the prescriber consider a change to a preferred product?</td>
<td>Yes: Inform provider of covered alternatives in class. <a href="http://www.orpdl.org">www.orpdl.org</a></td>
<td>No: Go to #3.</td>
</tr>
<tr>
<td>Message:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Preferred products do not require PA.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Preferred products are evidence-based reviewed for comparative effectiveness &amp; safety by the Pharmacy and Therapeutics (P&amp;T) Committee.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reports are available at:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><a href="http://pharmacy.oregonstate.edu/drug-policy">http://pharmacy.oregonstate.edu/drug-policy</a></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to

| Yes: Go to #4. | No: Pass to RPH; Deny for medical appropriateness. |
these treatments?

Contraindications to metformin:
- Known hypersensitivity
- Renal disease or renal dysfunction
- Acute or chronic metabolic acidosis
- Increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function)

Contraindications to sulfonylureas:
- Known hypersensitivity
- Increased risk of hypoglycemia

Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

4. Is the patient currently taking insulin?  
Yes: Go to #5  
No: Approve for up to 12 months.

5. Is the patient requesting exenatide (Byetta), liraglutide (Victoza) or albiglutide (Tanzeum) and is using basal insulin?  
Yes: Approve for up to 12 months.  
No: Go to #6.

6. Is the patient taking dulaglutide (Trulicity) and is using prandial insulin?  
Yes: Approve for up to 12 months.  
No: Pass to RPH; Deny for medical appropriateness.  
The safety and efficacy of other insulin formations and GLP-1 agonists have not been studied.

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.


Revision(s): 1/1/14
Initiated: 7/23/12, 1/1/12
Appendix 2: Specific Drug Information

**CLINICAL PHARMACOLOGY**
Albiglutide is a GLP-1 receptor agonist and augments glucose-dependent insulin secretion and slows gastric emptying.

**PHARMACOKINETICS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Bioavailability</td>
<td>NA</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>Not studied</td>
</tr>
<tr>
<td>Elimination</td>
<td>Vascular endothelium</td>
</tr>
<tr>
<td>Half-Life</td>
<td>5 days</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Proteolytic enzymes</td>
</tr>
</tbody>
</table>

**DOSE & AVAILABILITY**

<table>
<thead>
<tr>
<th>STRENGTH</th>
<th>ROUTE</th>
<th>FREQUENCY</th>
<th>DOSAGE:</th>
<th>RENAL ADJ</th>
<th>HEPATIC ADJ</th>
<th>Pediatric Dose</th>
<th>Elderly Dose</th>
<th>OTHER DOSING CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg or 50 mg</td>
<td>Subcutaneous</td>
<td>Once weekly</td>
<td>Give once weekly without regard to meals or time of day. Initiate at 30 mg initially and may be increased to 50 mg.</td>
<td>Monitor renal function in patients with renal impairment and report severe adverse gastrointestinal symptoms</td>
<td>None given</td>
<td>Not studied</td>
<td>No differences in overall safety and effectiveness</td>
<td>• If dose is missed, administer within three days of missed dose.</td>
</tr>
</tbody>
</table>

**DRUG SAFETY**

*Serious (REMS, Black Box Warnings, Contraindications)*:
- REMS: Due to risk of medullary thyroid carcinoma and risk of acute pancreatitis associated with albiglutide.
- Black box warning: Thyroid C-cell tumors have been seen in rodent studies with GLP-1 receptor agonists and it is unknown if albiglutide carries this same risk. Do not use in patients with a personal or family history of medullary thyroid carcinoma, Multiple Endocrine Neoplasia syndrome type 2.

Author: Kathy Sentena, Pharm.D.
**Warnings and Precautions:**

- Discontinue albiglutide if pancreatitis is suspected. Consider using other agents in patients with a history of pancreatitis.
- Hypoglycemia may occur when using albiglutide with insulin secretagogues or insulin. Consider lowering dose of insulin secretagogues or insulin when starting albiglutide.
- Discontinue albiglutide if hypersensitivity reactions occur.
- Monitor renal function in patients with renal impairment and report severe gastrointestinal reactions.
- Albiglutide is not recommended for patients with pre-existing severe gastrointestinal disease.

**Monitoring:** Monitor renal function in patients with renal impairment.

**Drug-Drug interactions:** No clinically significant drug interactions have been identified. Albiglutide has not been studied in combination with prandial insulin.

**Food-Drug Interactions:** No food-drug interactions have been identified.

**Pregnancy/lactation rating:** Category C. Albiglutide has not been adequately studied in pregnant women. Data are insufficient to recommend albiglutide in women who are lactating.

**ADVERSE REACTIONS**

Adverse reactions occurring in ≥10% of patients treated with albiglutide were upper respiratory tract infections, diarrhea, nausea, and injection site reactions.