CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208673Orig1s000

SUMMARY REVIEW
# Division Director Summary Review for Regulatory Action

<table>
<thead>
<tr>
<th>Date</th>
<th>(electronic stamp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>From</td>
<td>Jean-Marc Guettier, MD</td>
</tr>
<tr>
<td>Subject</td>
<td>Division Director Summary Review</td>
</tr>
<tr>
<td>NDA/BLA #</td>
<td>NDA 208673</td>
</tr>
<tr>
<td>Supplement #</td>
<td></td>
</tr>
<tr>
<td>Applicant</td>
<td>Sanofi Aventis US, LLC</td>
</tr>
<tr>
<td>Date of Submission</td>
<td>December 21, 2015</td>
</tr>
<tr>
<td>PDUFA Goal Date</td>
<td>August 21, 2016</td>
</tr>
<tr>
<td>Proprietary Name / Non-Proprietary Name</td>
<td>Soliqua/Insulin Glargne and Lixisenatide</td>
</tr>
<tr>
<td>Dosage Form(s) / Strength(s)</td>
<td>Solution for subcutaneous injection (100 units and 50 mcg per mL and 100 units and 33 mcg per mL)</td>
</tr>
<tr>
<td>Applicant Proposed Indication(s)/Population(s)</td>
<td>As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both glargine and lixisenatide is appropriate</td>
</tr>
<tr>
<td>Action/Recommended Action for NME:</td>
<td>Approval</td>
</tr>
<tr>
<td>Approved/Recommended Indication/Population(s)</td>
<td>SOLIQUA 100/33 is a combination of insulin glargine and lixisenatide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on a basal insulin (less than 60 units daily) or on lixisenatide.</td>
</tr>
</tbody>
</table>

### Material Reviewed/Consulted

<table>
<thead>
<tr>
<th>OND Action Package, including:</th>
<th>Names of discipline reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Officer Review</td>
<td>Suchitra Balakrishnan, MD PhD</td>
</tr>
<tr>
<td>Statistical Review</td>
<td>Jiwei He, PhD;</td>
</tr>
<tr>
<td>Pharmacology Toxicology Review</td>
<td>Feleke Estete, PhD</td>
</tr>
<tr>
<td>CMC Review</td>
<td>Muthukumar Ramaswamy, PhD; Yuesheng Ye, PhD</td>
</tr>
<tr>
<td>Microbiology Review</td>
<td>Maria Cruz-Fisher, PhD</td>
</tr>
<tr>
<td>Clinical Pharmacology Review</td>
<td>Sista Suryanarayana, PhD</td>
</tr>
<tr>
<td>OPDP</td>
<td>Charuni Shah, PharmD</td>
</tr>
<tr>
<td>DSI</td>
<td>Cynthia Kleppinger, MD</td>
</tr>
<tr>
<td>CDTL Review</td>
<td>Bill Chong, MD</td>
</tr>
</tbody>
</table>

OND=Office of New Drugs  
OPQ=Office of Pharmaceutical Quality  
OPDP=Office of Prescription Drug Promotion  
OSI=Office of Scientific Investigations  
CDTL=Cross-Discipline Team Leader  
OSE= Office of Surveillance and Epidemiology  
DEPE= Division of Epidemiology  
DMPEPA=Division of Medication Error Prevention and Analysis
Benefit-Risk Assessment
Benefit-Risk Summary and Assessment

Soliqua is a fixed combination drug product that combines the basal insulin, insulin glargine, with the GLP-1 receptor agonist, lixisenatide, into a single solution for injection. The solution contains a fixed amount of insulin glargine and lixisenatide per unit volume and dose adjustment for the individual drug components is not possible. The Soliqua product that will be marketed contains 1 unit of insulin glargine and 0.33 mcg of lixisenatide per 10 microliters of solution (i.e., 100 units and 33 mcg of insulin glargine and lixisenatide per mL, respectively). The other solution (100 units and 50 mcg per mL) proposed will not be approved.

The two active ingredients in Soliqua, insulin glargine and lixisenatide, are the active ingredients in Lantus and Adlyxin respectively, two approved products. Combining these two active ingredients in a single product may appear rational in that the two products are administered by injection, have a once daily frequency of administration and have complementary glucose lowering effects. However, Lantus and Adlyxin have diametrically opposite dosages. Lantus’ dosage is extremely flexible and customizable whereas Adlyxin dosage is not and is fixed at 20 mcg per day. The dosages of glargine and lixisenatide in Soliqua reflect neither Lantus nor Adlyxin dosage and were selected to accommodate the delivery of the two products in a single solution.

Use of Injectable Antidiabetics in the Care Setting

Antidiabetes drugs delivered by injection, such as GLP-1 receptor agonists and insulins, are most commonly used as third or fourth line options for patients inadequately controlled (HbA1c between 7 to 9%) on two or three oral agents belonging to the 8, currently marketed, oral anti-diabetic drug classes. GLP-1 receptor agonists are effective glucose lowering drugs, have a low inherent risk of hypoglycemia and are fairly straightforward to dose. Insulins are the most effective glucose lowering drugs, can cause hypoglycemia, and are more complicated to dose but their dose can be finely tuned to precisely meet the individual’s glucose lowering needs. Insulins are the preferred agents in patients with very poorly controlled blood glucose (e.g., HbA1c > 10%). Basal insulin and GLP-1 receptor agonist can be used together to treat patients not adequately controlled on either agent alone.

Role of Combination Antidiabetics in the Care Setting

Current professional guidelines recommend adding glucose lowering drugs one at a time and escalating glucose lowering therapy with more agents only in patients who, after 3 to 6 months, have not attained glycemic goal. Initiating two glucose lowering drugs at once is generally not recommended in the management of type 2 diabetes. Many patients (40 to 70% depending on the class and background co-administered drug) will tolerate and achieve optimal control, at least for some time, with addition of a single agent and exposure of these patients to the added risks of a second agent is not justified. The paradigm used in the landmark United Kingdom Prospective Diabetes Study trial was a sequential add-on trial and data to establish that starting two drugs at once confers added clinical benefits [i.e., improved outcomes or overall benefits to risk] are lacking. In fact, the wisdom of a strategy aimed at rapidly and aggressively controlling glucose, at all cost, was called into question by data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.
In the study, use of multiple drugs to rapidly target glucose normalization was found to be harmful to patients with established diabetes at high risk of cardiovascular disease. In addition it is unclear that benefits stemming from reducing the dose of one drug aren’t counterbalanced by risks associated with the presence of a second drug in the combination. For example in patients receiving Soliqua, the benefits gained by reducing the dose of GLP-1 on nausea and vomiting were offset by increased risks of hypoglycemia due to the insulin component. In light of these issues, antidiabetic fixed combination drug products are most appropriate for patients who have failed one of the components in the combination and require addition of the other drug component to manage their diabetes. The population of concurrent users will be; patients who have failed oral drugs and one of the component in the combination.

**Objectives and Main Results of the Soliqua Program**

The rule for fixed combination drug products at 21 CFR 300.50 states that “Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.”

The Soliqua clinical program was designed to address 21 CFR 300.50. The main clinical objectives of the program were to demonstrate that the two active ingredients in the product contributed to glucose lowering and that the risks associated with combining the two active ingredients would be additive and not synergistic. The applicant met these objectives. Specifically, the applicant demonstrated that each component in the combination contributes to improvement in glycemic control, the claimed effect, in trial EFC12404. At the end of 30 weeks, ~40 units/~17 mcg of Soliqua (insulin glargine/lixisenatide) was observed to reduce HbA1c to a greater extent than ~40 units of Lantus (insulin glargine) and 20 mcg of Adlyxin (lixisenatide). Soliqua was compared to a maximally effective dose of lixisenatide but was not compared to a maximally effective or optimal dose of insulin glargine (i.e., the comparison between Soliqua and Lantus was based on comparing the two products at an equivalent dose of insulin glargine). In the safety assessment, Soliqua was found to carry risks attributable to both the glargine (i.e., hypoglycemia) and lixisenatide components (i.e., GI-related adverse reactions, serious allergic adverse reactions, injection site reactions and immunogenicity related risks) and the estimate for these risks were found to be additive and not synergistic.

**Limitations on Clinical Utility**

Soliqua allows for delivery of two drugs in the form of a single injection but individual component drug dosing and titration is not possible with the product. This limits dosing flexibility. For example to address a risk related to dosing of one component (i.e., hypoglycemia with insulin) lowering the dose of both drugs in the combination is required (but may not be desired from an efficacy standpoint). The lack of dosing flexibility also made it difficult to clearly identify a patient population who could use this product. For example, subjects who are treated with both drugs in the form of Lantus and Adlyxin cannot receive equivalent doses of component drugs in Soliqua because the ratio is fixed and because only one approved dose of Adlyxin is marketed (the sole exception are those patients receiving exactly 60 units of glargine and 20 mcg of lixisenatide who could in theory receive the maximum Soliqua dose and would quickly need additional insulin). In addition, patients treated with either insulin glargine or lixisenatide in the form of Lantus or Adlyxin require reductions in the dose of either insulin glargine or lixisenatide to safely start Soliqua. It is important to note that dose reduction would not otherwise be

---

1 N Engl J Med 2008; 358:2545-2559
required when adding insulin glargine or lixisenatide individually in the form of Lantus or Adlyxin (e.g., refer to the Adlyxin Full Prescribing Information).

Insulin dosing in Soliqua is constrained by GLP-1 dosing and limited to a maximum of 60 units. Soliqua would therefore not be an appropriate therapy for patients with severe insulin resistance and very poor glycemic. These patients may require larger doses of insulin than can be delivered by Soliqua and a more flexible and customizable insulin dosing regimen than is offered by Soliqua. Finally, patients uncontrolled on the maximum dose of Soliqua would require additional injections of insulin and use of Soliqua would not offer a reduction in daily injection burden.

The lack of dosing flexibility posed a major challenge in defining a population for whom this combination product would be appropriate. An Endocrinologic and Metabolic Drug Advisory Committee was held on 25 May 2016 to discuss this very issue (refer to official transcript for details2). The clinical experts on the committee saw a utility of this product mainly for patients with inadequate control on a product containing one of the components in Soliqua. The main benefit the advisors noted was one of convenience (i.e., delivery of two injectable glucose lowering drugs using a single injection). Twelve members of the committee recommended approval of the product and two members did not recommend approval based on expected risks associated with introducing a two pen presentation in the healthcare setting.

Recommendations

Soliqua offers little benefits for patients with an HbA1c between 7 to 9% who are not on either drug products. Patients in this category who are insulin sensitive may not get to doses of Soliqua that are high enough to derive benefits (i.e., HbA1c reduction) from both components in the combination. Second, a majority of these patients could tolerate and reach glycemic goals using one of the approved GLP-1 agonist. In fact, some GLP-1 receptor agonist can be injected once weekly, have a similar short term (6 months) glucose lowering effect than Soliqua, are simpler to dose and have less risks of hypoglycemia or weight gain. For patients who tolerate a GLP-1 receptor agonist, it is difficult to justify why the use of two drugs injected daily and exposure to the risks of two drugs would be warranted. Soliqua is also not a good option for patients who have very poor glycemic control (HbA1c >10%). These patients are often severely insulin resistant, require large doses of insulin (i.e., doses of glargine beyond those offered by Soliqua) and frequent insulin dose adjustment to rapidly restore control and prevent complications (Hyperosmolar Hyperglycemic State). Soliqua dosing is insufficiently flexible for these patients and these patients should be treated with insulin alone.

I concur with the opinions of the clinical experts on the panel that this drug may be most useful to some patients who need improvement in glucose control and who are already receiving one component drug in the combination. While tighter glucose control could undoubtedly be achieved by administering the two drugs as separate products, some patients may fare better with a simpler, albeit not optimal, glucose lowering regimen. In that regard, Soliqua is similar to approved mixed insulin products. These products have limited dosing flexibility and do not represent an optimal way to dose either basal or prandial insulin. They are used when the objective is to simplify anti-diabetic therapy and they represent a convenient way to cover fasting blood glucose and post-prandial glucose for one meal of the day. Soliqua fills similar needs. Soliqua was associated with less nausea and vomiting than Adlyxin and in patients who cannot tolerate Adlyxin this drug could be used.

---

2 [http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm491062.htm](http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm491062.htm)
In light of these considerations, the indication that will be granted will be: **SOLIQUA 100/33 is a combination of insulin glargine and lixisenatide** and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on a basal insulin (less than 60 units daily) or on lixisenatide. This indication is warranted because contribution to claimed effect has been demonstrated for both components. Indications for combination generally name the specific components because efficacy of products can vary across class (e.g., GLP-1 drugs are not all equally effective). An exception was made for basal insulin since as a class these drugs has more customizable doses and similar effects in the range of doses proposed. Finally dose limits on insulin were imposed due to inherent limitations in dosing for the product.

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td>1. Chronic hyperglycemia is associated with a heightened risk of eye, kidney and peripheral nerve disease. Control of hyperglycemia over a 10 year period with sulfonylurea drugs and insulin reduced the risk of eye, kidney, and peripheral nerve disease in adult patients with type 2 diabetes in the UKPDS study. Control of hyperglycemia with insulin over 6 years resulted in similar findings in a smaller study of adult Japanese individuals with type 2 diabetes (Kumamoto Study). 2. There are multiple oral drugs (8 classes) indicated to improve glycemic control in adults with type 2 diabetes mellitus. 3. Drugs to treat diabetes are added sequentially as disease progresses. 4. Patients with type 2 diabetes whose glycemic control is not adequate with diet, exercise and a maximally effective/tolerated dose of one, two or three oral anti-diabetic agent require drugs delivered by subcutaneous injection to control hyperglycemia.</td>
<td>1. Improvement in glucose control captured using the change in HbA1c over six months is used as a substitute for clinical benefit to establish the efficacy of drugs to treat type 2 diabetes 2. Selection of agents to treat diabetes is based on individual patient characteristics, specific drug-related risks and patient tolerability. The most common first line agent is metformin. 3. In a large proportion of individuals (i.e., 40-70%) with an HbA1c between 7-9% addition of a single new drug will improve glycemia and will result in achievement of adequate control glucose (i.e., goals set by guidelines) over the medium term. 4. Drugs delivered via subcutaneous injection are typically reserved as third and fourth line options.</td>
</tr>
<tr>
<td>Current Treatment Options</td>
<td>1. Twice daily, Once daily or once weekly GLP-1 receptor agonist (Byetta, Victoza, Bydureon, Tanzeum, Trulicity, Adlyxin) 2. Basal insulin products (Lantus, Levemir, Degludec, NPH). Mixed insulin products (Humalog 50/50, Humalog 75/25, Novolog, Novolog 50/50, Novolog 70/30, Ryzodeg 70/30, Humulin R, Humulin 70/30, Novolin R, Novolin 70/30). Prandial insulin products (Humulin N, Novolin N, Humalog, Novolog, Apidra,</td>
<td>1. GLP-1 receptor agonists are effective at improving glycemic control, have a low inherent risk of hypoglycemia and weight gain, have simple dosing regimens, do not require self-monitoring of blood glucose for hypoglycemia or dose adjustment, and some can be injected at once weekly intervals (Trulicity and Tanzeum). 2. Insulins are the most effective and durable glucose</td>
</tr>
</tbody>
</table>
### Evidence and Uncertainties

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefit</strong></td>
<td>Afrezza (inhalation route)]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The lixisenatide and insulin glargine component in the Soliqua product were shown to contribute to the claimed effect of improvement in glycemic control in pivotal trial EFC12404.</td>
<td></td>
</tr>
<tr>
<td>2. In EFC12404 Soliqua (variable doses from 10 to 60 units of insulin glargine and 5 to 20 mcg of lixisenatide) provided greater HbA1c reduction than a maximally effective dose of Adlyxin (lixisenatide 20 mcg once daily) at the cost of a greater risk of hypoglycemia and worse weight control.</td>
<td></td>
</tr>
<tr>
<td>3. Soliqua provided numerically greater HbA1c reduction than sub-optimally dosed Lantus at the week 30 time point in treatment naïve patients and in patients inadequately controlled on a low dose of a basal insulin (mostly Lantus) at baseline. Doses of glargine in the Soliqua arm and Lantus were equivalent at trial end. Soliqua and Lantus had similar to slightly higher risk of hypoglycemia.</td>
<td></td>
</tr>
<tr>
<td>4. The two components in Soliqua target somewhat complementary glucose abnormalities.</td>
<td></td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td>Risks related to the use of Soliqua identified include; risk of common and serious GI adverse reactions, risk of serious allergic reactions, injection site reactions and hypoglycemia.</td>
</tr>
<tr>
<td>2. A risk of transient hyperglycemia associated with switching from Adlyxin or Lantus to Soliqua exists. Patients receiving the full 20 mcg dose of lixisenatide as Adlyxin will receive 5 mcg of lixisenatide when Soliqua is started (to ensure they do not start on too high a dose of glargine). Patients receiving any dose of insulin glargine above 30 units will have their dose of insulin reduced to 30 units (to ensure they don’t start on too high a</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The data in the application met the “claimed effect” regulatory requirements for fixed combination drug described in Section 300.50 of Title 21 of the Code of Federal Regulations.</td>
<td></td>
</tr>
<tr>
<td>2. The glucose lowering effect of Soliqua was greater than the glucose lowering effect of a maximally effective dose of Adlyxin.</td>
<td></td>
</tr>
<tr>
<td>3. Clinical superiority of Soliqua to Lantus was not demonstrated as the dose of Lantus was not optimized and the trial was of insufficient duration to adequately address this question (see discussion in Efficacy).</td>
<td></td>
</tr>
<tr>
<td>4. Similar to a pre-mixed insulin the product combines a product that controls fasting glucose (lantus) with a product (lixisenatide) that controls glucose excursion after one meal of the day and to a lesser extent fasting glucose.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Soliqua carries risks attributable to both the glargine (hypoglycemia) and lixisenatide components (GI-related adverse reactions, allergic adverse reactions, injection site reactions and immunogenicity related risks). It cannot be concluded that Soliqua is safer than individual products. For example while patients on Soliqua had fewer nausea and vomiting events than patients on Adlyxin they had many more hypoglycemic events.</td>
<td></td>
</tr>
<tr>
<td>2. The risk of transient hypoglycemia during product switch was evaluated for the population enrolled in the clinical</td>
<td></td>
</tr>
<tr>
<td>Dimension</td>
<td>Evidence and Uncertainties</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Risk Management</td>
<td>1. Potential risks associated with a 2 pen product presentation</td>
</tr>
<tr>
<td></td>
<td>2. Labeling will be used to mitigate against product related risks including but not limited to risks of dosing errors, GI adverse reaction, hypoglycemia, hypersensitivity and injection site</td>
</tr>
<tr>
<td>Dimension</td>
<td>Evidence and Uncertainties</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>reactions.</td>
</tr>
<tr>
<td></td>
<td>3. No risks identified require risk management beyond labeling to warrant consideration of a Risk Evaluation and Mitigation Strategy (REMS).</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 4017038
1. Background

On December 21, 2015 Sanofi Aventis US LLC submitted a New Drug Application (NDA) for the Fixed Combination Drug Product, Soliqua, pursuant to section 505(b)(1) of the Federal Food Drug and Cosmetic Act. Soliqua combines the basal insulin, glargine, with the GLP-1 receptor agonist, lixisenatide into one dosage form, a solution for injection. The applicant is seeking to indicate Soliqua as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate.

To my knowledge, Soliqua is the first Fixed Combination Drug Product that combines an active ingredient whose dose is titrated to effect when used individually (insulin glargine) with another active ingredient whose dose is fixed when used individually (lixisenatide).

Antidiabetic combinations have generally combined active ingredients dosed in the same fashion\(^3\) and combined doses of active ingredients already established to be effective\(^4\). Soliqua differs in both of these respects. In Soliqua, the lixisenatide dose is titrated within a proposed dose range (i.e., 5-20 mcg) to accommodate basal insulin dosing and the lixisenatide dose range proposed includes mostly unapproved lixisenatide doses (i.e., all lixisenatide doses below 20 mcg per day). This dosing regimen contrasts with the dosing regimen for the approved lixisenatide product, Adlyxin, which has a recommended dose of 20 mcg once per day. In addition in Soliqua, the upper insulin glargine dose is capped at 60 units to accommodate GLP-1 receptor agonist dosing and increasing glargine dose beyond the maximally effective and safe dose of lixisenatide (i.e., 20 mcg per day) is not possible. This contrasts with the dosing regimen for the approved insulin glargine product, Lantus, which has no upper maximally effective dose and no imposed upper limit on dosing.

The proposed Soliqua product offers limited flexibility in dosing individual components compared to the single ingredient products (i.e., Lantus and Adlyxin) and this reality limits the clinical utility of the product. For example, a patient who is not controlled on the full therapeutic dose of lixisenatide as Adlyxin (20 mcg per day) and needs intensification of therapy with a basal insulin cannot be switched to the full dose of lixisenatide when using Soliqua because of the risk of hypoglycemia secondary to “overdose” of the insulin component. Lixisenatide dose reduction is not required, or indeed desired, when dosing lixisenatide (Adlyxin) and glargine (Lantus) products individually in this clinical scenario. Similarly a patient receiving more than 20 units of glargine as Lantus and who needs intensification of diabetes therapy with a GLP-1 receptor agonist could not be switched to their full dose of insulin glargine when using Soliqua because the starting dose of lixisenatide

---

\(^3\) An active ingredient delivered as a fixed dose with another active ingredient delivered as a fixed dose (e.g., oral anti-diabetic combinations, oral anti-hypertensive combinations) or an active ingredient whose dose is individually titrated dose with another active ingredient whose dose is titrated (e.g., a pre-mix insulin products that combine a basal insulin with a meal-time insulin).

\(^4\) E.g., an approved dose of metformin with an approved dose of a DPP-4 inhibitor.
would be too high. Again, insulin glargine dose reduction is neither necessary nor desired in this clinical scenario. Third, the product is ill suited to patients receiving doses of glargine in excess of 60 units since the maximum amount of glargine that can be delivered in the Soliqua product is 60 units. Finally, individual dose adjustment of the glargine or lixisenatide components for product specific tolerability issues is not possible with Soliqua.

The proposed 2 pen product presentation is counterintuitive as it makes use of a higher product strength to deliver lower doses of Soliqua and use of a lower product strength to deliver higher doses of Soliqua. Healthcare workers would have to be able to readily recognize this to avoid inappropriate dispensing and use of the product. to use the product safely prescribers will also have to be aware that Soliqua contains two active ingredients (i.e., to prevent potentially duplicative therapies or using an unapproved dose of one or the other product).

Finally, correct use of Soliqua cannot be inferred from prior familiarity with use of either an insulin product or a GLP-1 agonist product. First, insulin doesn’t have an upper dose limit and upward insulin dose titration can continue almost indefinitely in extremely insulin resistant individuals. Soliqua has an upper insulin dose limit and titration of insulin beyond 60 units of insulin is not possible with this product. Second, GLP-1 agonists are dosed in discrete steps and the recommended effective dose is reached quickly. In Soliqua the GLP-1 component is dosed on a near continuous scale and the marketed effective dose of lixisenatide isn’t reached until the maximum dose of the product is reached. Thus correct use of Soliqua will require prescribers familiar with using either insulin or GLP-1 to be able to note how Soliqua dosing differs from these products and to change their prescribing habits accordingly.

Clinical utility and potential medication errors that would arise as a result of the product presentation were the main issues in this application and will be the focus of my review.

Proposed Product, Presentations and Uses

Soliqua is a Fixed Combination Drug Product (FCDP) that combines two approved active pharmaceutical ingredients (insulin glargine and lixisenate) into a single dosage form (i.e., a solution for injection). The applicant proposes to market two product “strengths”; a 2 units to 1 mcg fixed ratio solution of insulin glargine to lixisenate (i.e., a 2:1 fixed ratio solution) and a 3 units to 1 mcg fixed ratio solution of insulin glargine to lixisenate (i.e., a 3:1 fixed ratio solution).

The proposed presentation for the two strengths are two distinct pre-filled, multi-dose, disposable, manually operated, autoinjector devices; PEN A, in a peach yellow color, for the 2:1 fixed ratio solution and PEN B, in an olive green color, for the 3:1 fixed ratio solution. A graphic representation of the two devices reproduced from Dr. Ramaswamy’s review is shown below.
Each pen delivers a volumetric dose of solution. PEN A delivers a minimum volumetric dose of 10 microliters, which contains 1 unit and 0.5 mcg of insulin glargine and lixisenatide respectively, and a maximum volumetric dose of 400 microliters, which contains 40 units of insulin glargine and 20 mcg of lixisenatide respectively. PEN B delivers a minimum volumetric dose of 10 microliters, which contains 1 unit and 0.33 mcg of insulin glargine and lixisenatide respectively, and a maximum volumetric dose of 600 microliters, which contains 60 units of insulin glargine and 19.8 mcg of lixisenatide respectively. The dose for both pens can be increased by 10 microliter increments and the units on the pen dial denote glargine units only.

The 2:1 fixed ratio solution (i.e., PEN A) is intended for patients who require less than 40 units of insulin per day.
- The recommended starting dose for patients requiring less than 25 units of “basal” insulin per day would be a volumetric dose containing 10 units and 5 mcg of insulin glargine and lixisenatide respectively.
- The recommended starting dose for patients requiring between 25 and 40 units of “basal” insulin per day would be a volumetric dose containing 20 units and 10 mcg of insulin glargine and lixisenatide respectively.

The 3:1 fixed ratio solution (i.e., PEN B) is intended for patients who require between 41 and 60 units of basal insulin per day.
- The recommended starting dose for patients requiring more than 40 units of “basal” insulin per day and who are not already on the 2:1 fixed ratio solution (i.e., PEN A) would be a volumetric dose containing 30 units and 9.9 mcg of insulin glargine and lixisenatide respectively.
- The dose for patients already on the maximum volumetric dose for PEN A (i.e., 40 units and 20 mcg of insulin glargine and lixisenatide respectively) and who need additional glucose lowering would be a volumetric dose containing 40 units and 13.2 mcg of insulin glargine and lixisenatide respectively. A switch between PEN A and PEN B results in a 34% lixisenatide dose reduction by design.

Regulatory Issues

An investigational new drug application (IND 105157) for a product combining insulin glargine and lixisenatide for the treatment of Type 2 DM was opened on April 9, 2009.
The Agency questioned the rationale and voiced concerns about the loss of dosing flexibility that would potentially arise when combining two products with inherently dissimilar dosing regimens in a single dosage form (i.e., a titratable product with a fixed dose product). Insulin glargine is administered once daily, the dose is titrated to the individual’s needs and the product has no maximally effective dose. Individualization of insulin dose is important from both a safety (reduction in risk of hypoglycemia) and efficacy (increasing the dose in patients who do not respond) perspective. Lixisenatide is also administered once daily but the only dose established effective for the treatment of adults with type 2 diabetes mellitus is 20 mcg.

The presentation considered was the single cartridge pen injector presentation described above. This presentation delivers glargine and lixisenatide together and the doses of each product are determined by the concentration of each product in the solution and the volume of solution injected. In this configuration, the dose of one product is dependent on the dose of the other and individual product titration is not possible. The maximal dose of the combination product is limited to 20 mcg per day. The major concerns raised by this presentation were related to the impact of loss of dosing flexibility on efficacy and safety and resultant loss of clinical utility for the intended chronic use setting.

The applicant opted for the later presentation.

2. Product Quality

Dr. Muthukumar Ramaswamy the technical lead for the application recommends approval as there are not CMC or device issues that preclude approval.

The two active pharmaceutical ingredients (drug substances) in Soliqua are lixisenatide and insulin glargine. The applicant referenced NDA 021081 (insulin glargine) and NDA 206538 (lixisenatide) for all CMC information on the drug substances in Soliqua.

Lixisenatide is a synthetic peptide derived from the exendin-4 hormone. The primary sequence is 44 amino acids in length and includes six lysine residues at the C-terminal end of the molecule that were added to prevent degradation of the peptide by dipeptidyl peptidase-4 and increase the peptide’s residence time in circulation. The lixisenatide drug substance is manufactured by chemical synthesis.
Insulin glargine is an analogue of human insulin whose primary structure includes a 21 amino acids A chain and a 32 amino acids B chain linked to each other through disulfide bonds. The insulin glargine drug substance is manufactured by recombinant DNA technology from the non-pathologic K12 *Escherichia Coli* strain.

The Soliqua product is a sterile solution for injection with two proposed strengths: 100 units of glargine and 50 mcg of lixisenatide per mL and 100 units of glargine and 33 mcg of lixisenatide per mL. It should be noted that the lower concentration solution will be used to administer higher doses of the product which is counterintuitive and could lead to error in prescribing and dispensing.

The solution contains the following excipients; % glycerol methionine metacresol zinc and water for injection. Hydrochloric acid sodium hydroxide All excipients comply with compendial requirements.

The primary packaging material consists of clear, colorless 3 mL cartridges (glass type I) closed with plunger stoppers rubber) on one side and flanged caps (aluminum). The cartridge is irreversibly integrated into a fixed dose disposable pen-injector.

The pen-injector to be used for Soliqua administration is a manual, pressure operated, multi-dose, injector device designed to deliver variable volumetric doses of Soliqua solution. A new needle is attached prior to each dose and a priming step is required with the first use. The two different product strengths are to be presented as different color pen injectors; a peach yellow color pen (i.e., PEN A) for the 100 units of glargine and 50 mcg of lixisenatide per mL strength and an olive green colored pen for the 100 units of glargine and 33 mcg of lixisenatide per mL (i.e., PEN B).

The review of the engineering of the devices was completed by the Center for Devices and Radiological Health and no issues on the technical aspects of the devices that would preclude were identified.

The drug product manufacturing processes and in-process controls were reviewed in details by Drs. Muthukumar Ramaswamy, Yuesheng Ye, and no issues precluding approval were identified. Dr. Vipulchandra Dholakia assessed the proposed drug product manufacturing facilities. No concerns that would impact approvability of Soliqua were identified in this assessment and sites involved in drug substance and product manufacturing were deemed acceptable.

I concur with the conclusions reached by the product quality review team that the identity, potency as well as chemical and microbial purity of Soliqua will be assured in manufacturing.
Stability testing supports an expiration date of 18 months for the drug product when stored between 2 to 8°C. In use stability testing supports use of the product for up to 14 days when stored at room temperature (below 30°C). There are no outstanding CMC/Device issues.

3. Nonclinical Pharmacology/Toxicology

Drs. Eshete and Bourcier have reviewed nonclinical pharmacology and toxicology studies in details. Sanofi cross-referenced the nonclinical information in the insulin glargine (NDA: 021081) and lixisenatide (NDA: 208471) applications to support the Soliqua application. I concur with the conclusions reached by the pharmacology/toxicology review team that there are no outstanding pharmacology/toxicology issues that preclude approval of Soliqua.

4. Clinical Pharmacology

I concur with the conclusions reached by Dr. Suryanarayana Sista the clinical pharmacology/biopharmaceutics reviewer for the application that there are no outstanding clinical pharmacology issues that preclude approval. The findings and labeling recommendations made based on the clinical pharmacology evaluation are summarized in the Dr. Sista’s review. Refer to Dr. Chong’s CDTL for a summary of the clinical pharmacology findings.

5. Clinical Microbiology

I concur with the clinical microbiology reviewer for the application that there are no outstanding clinical microbiology issues that preclude approval.

6. Clinical/Statistical-Efficacy

The efficacy of glargine (dose individually titrated to meet metabolic needs) and lixisenatide (20 mcg once daily) to improve glycemic control were established in trials supporting the approval of NDAs 021081 and 208471 respectively.

The principal efficacy objective of the Soliqua phase 3 development program was to demonstrate that each active drug component of the fixed combination drug product contributes to improving glycemic control. Included in this main objective was the secondary objective of demonstrating that lixisenatide doses below the approved dose of 20 mcg once daily had an effect on long-term glucose control when co-administered with insulin. These objectives were mainly evaluated in trial EFC 12404.

EFC12404: Adults Inadequately Controlled on Metformin +/- another Oral Drug
EFC 12404 was a randomized, open-label, multi-center, multi-national, 3 arms, parallel-group, active controlled trial comparing Soliqua (N=469) to Lantus (N=467) and Adlyxin (N=234). The endpoint was at 30-weeks and the outcome measured across the three groups was the change from baseline in hemoglobin A1c.

Subjects were eligible to participate if they had type 2 diabetes mellitus for at least a year, were on metformin alone (≥1500 mg per day) or metformin combined with another oral anti-diabetic drug, had an HbA1c between 7 and 10%, had not been previously treated with insulin and had not discontinued a GLP-1 for tolerability or efficacy reasons in the past. Subjects receiving an anti-diabetic drug in addition to metformin before the screening visit, discontinued that drug in a 4-week run-in phase.

The starting dose in the Soliqua arm was 10 units of insulin glargine and 5 mcg of lixisenatide respectively. The starting dose in the Lantus arm was 10 units of insulin glargine (the recommended starting dose in the product label) and the starting dose in the Adlyxin arm was 10 mcg of lixisenatide (the recommended starting dose in the product label).

Soliqua and Lantus doses could be adjusted weekly based on the median glucose value obtained at the point of care over the three days which preceded the visit. The algorithm for dose adjustment for both products was identical and targeted a morning fasting plasma glucose between 80 and 100 mg/dL. The dose of both products was to be increased by 2 dose steps for a median glucose greater than 100 mg/dL or 4 dose steps for a median glucose greater than 140 mg/dL, respectively. The maximum weekly dose increase was thus limited to 4 units of insulin glargine and 2 mcg (or 1.3 mcg depending on the pen) of lixisenatide in the Soliqua group and 4 units of insulin glargine in the Lantus group.

Subjects randomized to Adlyxin increased the dose of lixisenatide to 20 mcg per day two weeks after starting the drug, in accordance with the Adlyxin product label.

The trial schedule included; a screening period, a 4-week run-in period where metformin dose was increased to achieve a maximally effective dose (2000 mg per day) and oral drugs were discontinued, a randomization visit for individuals meeting specific fasting plasma glucose and metformin dose criteria, a 30 week treatment period and a 3-day post-treatment follow-up period.

The primary outcome measure was the change in HbA1c between baseline and trial end. The applicant’s main objective was to demonstrate that Soliqua would provide superior HbA1c reduction over 30 weeks compared to Adlyxin and non-inferior HbA1c reduction over 30 weeks compared to Lantus (non-inferiority margin set at 0.3%).

One main objective was to demonstrate that the insulin component in Soliqua contributed to the claimed effect (i.e., comparison versus Adlyxin). The other objective was to demonstrate that the combination of lixisenatide and glargine was not unacceptably worse than glargine alone by a margin of 0.3%. The clinical logic behind this objective is difficult to follow. Why
would a prescriber use two products (Soliqua) when they could achieve clinically similar glycemic control with a single product (Lantus)?

The trial was not designed to establish that Soliqua would be more efficacious, safer or better tolerated than Lantus but simply to establish that each component in Soliqua contributes to the claimed effect (i.e., to improve glycemic control). In light of the fact that Lantus and Soliqua are titrated to effect, the applicant did not believe they could feasibly demonstrate superior HbA1c reduction with Soliqua over Lantus. They believed patients randomized to Soliqua would achieve similar HbA1c reduction with less glargine than patients randomized to Lantus. Achieving similar HbA1c reduction with less glargine would provide evidence that the GLP-1 component in Soliqua was contributing to the claimed effect of HbA1c reduction. It is also important to emphasize that the timing for the assessment (relatively short term trial) and the algorithm for dose adjustment artificially constrained Lantus efficacy in this study. While this was important for the purpose of demonstrating contribution of the GLP-1 component in Soliqua to the claimed effect (i.e., comparison versus Lantus), it limits the generalizability and clinical relevance of the findings for the Soliqua/Lantus comparison. In the clinical setting Lantus dose increase is not limited to 4 units per week, Lantus efficacy does not plateau by Week 30 and maximum Lantus dose is not limited to 60 units.

Demographics (sex differences were observed) and disease characteristics were generally balanced between groups at baseline (refer to Table 9 in Dr. Balakrishnan’s review). The mean age of participants was 59 years, 47 to 57% of patients were men, 90% were White and 5 to 7% were Black. Half of the population had a BMI of 32 kg/m$^2$ or greater (i.e., obese range). The mean duration of diabetes was ~8 years, ~58% were using two oral anti-diabetic drugs at screening, the median daily dose of metformin at randomization was 2000 mg and >99% of the population had mean baseline eGFR in the normal to mild range (i.e., greater than 60 mL/min/1.73 m$^2$).

The primary analysis relied on a Mixed Model (MMRM) with treatment groups (Soliqua, Lantus, Adlyxin), HbA1c randomization strata (<8.0%, ≥ 8.0%) at Visit 4 (Week -1), second antidiabetic drug use at screening randomization strata (Yes, No), visit (Week 8, 12, 24, and 30), treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate. The primary analysis population was the modified intent to treat population (subjects randomized who received one dose of the intervention and had one post-baseline assessment).

A description of the patient disposition is shown in Table 3 of Dr. He’s review. More participants in the Adlyxin arm discontinued treatment due to an adverse event compared to subjects randomized to Soliqua or Lantus. Approximately 6 to 12% of participants were missing an HbA1c measurement at Week 30 in each treatment group. This amount of missing data was determined to be unlikely to impact overall study conclusion (refer to Dr. He’s review for discussion).
At trial end, the two drug combination product (Soliqua) provided numerically greater HbA1c reduction than either of the single drug products (Adlyxin and Lantus). This establishes that each of the components in Soliqua contributes to the claimed effect.

**Table 1: Mean change in HbA1c (%) from baseline and Differences between Groups**

<table>
<thead>
<tr>
<th>Study</th>
<th>Arms (n)</th>
<th>Baseline HbA1c</th>
<th>LS mean change in HbA1c from baseline</th>
<th>LS mean treatment difference (95% CI)</th>
<th>p-value for superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFC12404</td>
<td>Soliqua (467)</td>
<td>8.08</td>
<td>-1.63</td>
<td>-0.29 (-0.38, -0.19)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Lantus (464)</td>
<td>8.08</td>
<td>-1.34</td>
<td>-0.78 (-0.90, -0.66)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Adlyxin (233)</td>
<td>8.13</td>
<td>-0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soliqua versus Lantus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soliqua versus Adlyxin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dosing and Interpretability of Observed Effect Size Difference between Soliqua and Lantus*

The proportion of participants who achieved the fasting plasma glucose target was similar between Soliqua (blue bars) and Lantus (red bars) in the study [shown in the Figure 5 of Dr. Balakrishnan’s review (reproduced below)]. The majority of participants (i.e., ~65%) did not reach the protocol intended fasting glucose target by trial end and a plateau in the dose of Lantus was not achieved. Product tolerability (i.e., hypoglycemia risk) did not account for this finding as hypoglycemia risk was low and similar between the two arms. The Lantus dosing algorithm used in the trial was very conservative (~ 1 unit increment of glargine per week) and this likely explains the findings. These data call into question the adequacy of Lantus dosing in the trial and colors the interpretation of the effect size comparison between Soliqua and Lantus. How does one interpret the clinical meaningfulness of numerical superiority of Soliqua versus Lantus if Lantus was not optimally dosed?
The mean doses of insulin glargine were similar in the Soliqua (Blue Bar) and Lantus (Red Bar) arms throughout the study. At trial end, the baseline glargine dose was increased by 30 units (i.e., delta) in both arms (reproduced from Figure 5 in Dr. Balakrishnan’s review). Since glargine doses between arms are equivalent, differences in HbA1c between Soliqua and Lantus can be reasonably attributed to the lixisenatide component demonstrating the lixisenatide component in Soliqua contributes to the glucose lowering effect.
This however colors the interpretability of the effect size comparison between Soliqua and Lantus. Is the numerical superiority of Soliqua versus Lantus simply the result of poor Lantus dosing? As stated before in the care setting Lantus dose increase is not limited to a few units per week, the time to reaching an optimal Lantus dose is not limited to 30 weeks and the upper dose limit for Lantus is not limited to 60 units. As was stated before all three of these constraints were placed on Lantus dosing in this trial and the generalizability of the trial findings to the care setting are limited.

The trial does not provide compelling evidence that Soliqua is clinically superior to Lantus at improving glycemic control in adults with Type 2 diabetes mellitus because it is highly probable that a different outcome would have been observed had a less conservative Lantus dosing algorithm been utilized, a different assessment time point been used (e.g., a year) or had no limits been placed on maximal Lantus dose.

**Secondary Endpoints**

Drs. He, Chong and Balakrishnan have reviewed analyses for secondary glycemic endpoints (i.e., fasting plasma glucose, proportion of subjects reaching HbA1c threshold and 2-hour post-prandial glucose for the meal immediately following injection of products etc). The results of these analyses were consistent with the primary analyses and in keeping with the expected pharmacokinetic and pharmacodynamic effects of each therapy (i.e., Lixisenatide alone had almost no effect on fasting plasma glucose 24 hours after injection, Lixisenatide had an effect on the 2-hour post-prandial glucose value for the meal that immediately followed injection of the GLP-1 agonist). At the end of trial a large proportion of patients in
both the Soliqua and Lantus arms had an HbA1c below 7% (i.e., 74 and 60 percent respectively). This begs the question, if 60% of patients can achieve glycemic control with one drug why would they need two drugs?

The applicant evaluated effects of Adlyxin, Soliqua and Lantus on body weight in secondary analyses (see Table 5 in Dr. He’s review). It was previously established that use of Adlyxin results in a small amount of weight loss over 6 months when combined with metformin. In EFC12404 numerical differences in body weight were observed between Adlyxin, Soliqua and Lantus at Week 30. Subjects randomized to Adlyxin and Soliqua lost an average of 2.3 kg and 0.29 kg respectively from a baseline of ~90 kg, whereas subjects randomized to Lantus gained an average of 1.1 kg from a baseline bodyweight of 90 kg. The differences between Soliqua and both comparators were nominally statistically significant. Whether observed numerical differences in body weight were perceptible or had an impact on daily function at 30 week was not captured.

**EFC12405: Adults Inadequately Controlled on Basal Insulin +/- one or two OAD**

EFC 12405 was a randomized, open-label, multi-center, multi-national, 2 arms, parallel-group, active controlled trial comparing Soliqua (N=367) to continuing basal insulin with Lantus (N=369) in patients who were not adequately controlled at baseline an antidiabetic regimen that included low doses of a basal insulin. The endpoint was at 30-weeks and the outcome measured was the change from baseline in hemoglobin A1c.

Subjects were eligible to participate if they had type 2 diabetes mellitus for at least a year, were on basal insulin for at least 6 months, were on a specific basal insulin and injection frequency for at least 3 months and were receiving a stable dose between 15 to 40 units of basal insulin per day for at least 2 months prior to the screening visit. Patients could also be receiving one or two oral antidiabetic drug(s) including metformin or a sulfonylurea, meglitinide, DPP-4 inhibitor or SGLT-2 inhibitor. At screening, HbA1c had to be between 7.5% and 10%. Subjects who had used insulins other than basal insulins were excluded. Subjects with a history of poor tolerability to GLP-1 and hypoglycemia unawareness were also excluded. Subjects receiving oral anti-diabetic drugs other than metformin before the screening visit discontinued these drugs in a 6-week run-in phase.

The trial schedule included; a screening period, a 6-week run-in period where everybody was switched to Lantus and oral drugs other than metformin were discontinued, a randomization visit for individuals meeting specific fasting plasma glucose and Lantus dose criteria, a 30 week treatment period and a 3-day post-treatment follow-up period.

The starting dose in the Soliqua arm was 20 units of insulin glargine and 10 mcg of lixisenatide respectively (PEN A) for patient requiring less than 30 units of Lantus per day at the end of the run-in phase and 30 units of glargine and 10 mcg of lixisenatide (PEN B) for patients requiring at least 30 or more units of Lantus per day at the end of the run-in period.
The starting dose of Lantus in the Lantus arm was the same dose in units that had been used in the run-in phase (mean dose was 35 units).

Soliqua and Lantus doses could be adjusted weekly based on the median glucose value obtained at the point of care over the three days which preceded the visit. The algorithm for dose adjustment for both products was identical to the one used in EFC12404. The dose increments in lixisenatide differed based on the PEN device used with more lixisenatide being delivered in PEN A than PEN B per dose increment.

All of the issues related to the adequacy of the algorithm with respect to ensuring optimal Lantus dosing discussed above also pertain to this trial. In this trial participants were not optimally controlled on an average Lantus dose of 35 units per day at randomization. Patients receiving a Lantus dose close to the average dose were limited to a Lantus dose increase of 25 units over the approximately 180 day trial period before they reached the trial imposed Lantus dose cap of 60 units. Form a clinical perspective, this level of Lantus dose increase per unit time is infinitesimally small (i.e., it averages <1 unit increase per week) and isn’t likely to result in optimal Lantus dosing. Again, the proportion of the trial population reaching intended fasting plasma glucose target was low (~30%) and glargine dose at Week 30 was equal in the Lantus and Soliqua arm (refer to Figure 5 in Dr. Balakrishnan’s review).

The primary outcome measure was the change in HbA1c between baseline and trial end. The applicant’s main objective was to demonstrate that Soliqua would provide superior HbA1c reduction over 30 weeks compared to continuing basal insulin.

Demographics (sex differences were observed) and disease characteristics were generally balanced between groups at baseline (refer to Table 9 in Dr. Balakrishnan’s review). The mean age of participants was 60 years, ~47% of patients were men, 92% were White and 6% were Black. The median duration of diabetes was ~11 years. Half of the population had a BMI of 31 kg/m\(^2\) or greater (i.e., obese range). Approximately 63% and 22% were using Lantus and NPH insulin respectively at screening and the median daily dose of basal insulin at randomization was 30 units. 90% of the population was on metformin and >96% of the population had mean baseline eGFR in the normal to mild range (i.e., greater than 60 mL/min/1.73 m\(^2\)).

Disposition is summarized in Table 7 of Dr. He’s review. More subjects on Soliqua discontinued prematurely (92% versus 96%). There were more discontinuations due to adverse events (GI tolerability and hypoglycemia) in the Soliqua group compared to the Lantus group. The major reasons for discontinuation and missing observations at trial end thus did not appear random but product-related. Dr. He critically reviewed the primary analysis method. Subjects were not followed after discontinuation and sensitivity analysis based on imputation methods from data collected in retrieved dropouts could not be conducted. In light of the small amount of missing observations it was deemed unlikely that overall conclusions of statistical superiority of Soliqua over Lantus would have changed had all patients randomized been followed to trial completion.
The results of the primary analysis are shown below. Over 30 weeks, randomization to Soliqua resulted in numerically greater HbA1c reduction than randomization to continuing pre-trial therapy with basal insulin in the form of Lantus. The trial showed Soliqua was statistically superior to Lantus in a setting where final achieved glargine dose was equivalent between intervention groups. This trial again serves to demonstrate that the GLP-1 component in the combination contributed to the effect. As stated above Lantus dosing was artificially constrained in the trial and was not optimized therefore one cannot conclude that Soliqua is clinically superior to Lantus for improving glycemic control even in this setting.

**Table 2: Mean change in HbA1c (%) from baseline and Differences between Groups**

<table>
<thead>
<tr>
<th>Study</th>
<th>Arms (n)</th>
<th>Baseline HbA1c</th>
<th>LS mean change in HbA1c from baseline</th>
<th>LS mean treatment difference (95% CI)</th>
<th>p-value for superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFC12405</td>
<td>Soliqua (467) Lantus (464) Soliqua versus Lantus</td>
<td>8.07 8.08</td>
<td>-1.13 -0.62</td>
<td>-0.52 (-0.63, -0.40)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Numerical differences across other glycemic and non-glycemic variables including; changes in 2-hour post-prandial glucose for the meal immediately following injection, and changes in body weight were reported in secondary analyses. The results of these analyses are consistent with the primary analysis in overall direction. Although the effects on these endpoints were consistent with expected pharmacology of each interventional product, the applicant did not capture the clinical importance or relevance of the observed small numerical differences in these parameters to the adult patient with type 2 diabetes. It is for example unclear that the difference in body weight of, on average, 1.6% observed at 30 weeks confers an important benefit (improved well-being, function or other parameter) or that it persists over time as disease progresses and therapies are intensified. Weight loss with GLP-1 agonist product comes at the cost of increased GI side effects (nausea, vomiting and diarrhea) which could offset any gain in quality of life attributed to weight loss per se.

## 7. Safety

Drs. Chong and Balakrishnan (refer to Section 7 of the review) have summarized the general safety findings for the combination product. The main safety analyses relied on a dataset which pooled safety data collected in the phase 2/3 trials to support the fixed combination product NDA (i.e., trials ACT12374, EFC12404 and EFC12405). EFC12404 was the only trial which included an Adlyxin comparator arm. Overall 992, 992 and 233 received at least one dose of Soliqua, Lantus and Adlyxin in the combination product NDA. The main safety objective for the NDA was to characterize very common (incidence of greater than 1/10) and common (incidence greater than 1/100) product-related risks associated with the combination product per se and the size of the safety database and exposure duration (median ~ 6 months) is sufficient to achieve this objective. The size and duration of exposure

Reference ID: 4017038
in this NDA is insufficient to characterize rare or very rare product-related risks. Rare events attributable to each of the components in the combination were characterized in applications for products containing single active pharmaceutical ingredient (Lantus and Adlyxin).

The major risks for the individual components in the combination are described in the current Adlyxin (lixisenatide) and Lantus (glargine) product labels. Rare, serious lixisenatide-related adverse reactions include; hypersensitivity/anaphylaxis reactions, pancreatitis, hypoglycemia when combined with insulin or a sulfonylurea and acute kidney injury. Common drug related risks associated with lixisenatide include gastrointestinal adverse reactions (nausea, vomiting) and injection site reactions. Serious glargine-related adverse reactions include; hypoglycemia, hypersensitivity reactions and fluid retention and heart failure when used with PPAR gamma receptor agonists. Common drug related risks include; injection site reaction, edema and weight gain.

In the development program, major safety findings including deaths (n=3, n=6 and n=1 for Soliqua, Lantus and Adlyxin) and serious adverse reactions (4.7%, 4.3% and 4.0% for Soliqua, Lantus and Adlyxin) were similar between intervention arms. More subjects randomized to Soliqua (2.8%) discontinued due to an adverse reaction compared to subjects randomized to Lantus (1.2%). GI adverse reactions (Nausea, vomiting), injection site reaction (urticaria) and hypoglycemia terms (dizziness, confusional states, hypoglycemic unconsciousness) accounted for discontinuations (refer to Table 30 in Dr. Balakrishnan’s review).

**Hypoglycemia**

Hypoglycemia related adverse reactions were common adverse reactions in patients randomized to drugs containing insulin glargine (i.e., Soliqua and Lantus). Events of a self-measured glucose of < 70 mg/dL accompanied with one or more symptom consistent with hypoglycemia was reported in 27%, 26% and 6% of patients randomized to Soliqua, Lantus and Adlyxin (refer to Table 32 in Dr. Balakrishnan’s review). Severe hypoglycemia was rare and only reported in patients randomized to Soliqua and Lantus (4 events on Soliqua and 2 events on Lantus). Soliqua and Lantus carry a greater risk of hypoglycemia than Adlyxin.

**Gastrointestinal Adverse Reactions**

Gastrointestinal adverse reactions were common reactions in patients randomized to drugs containing lixisenatide (i.e., Adlyxin and Soliqua). Nausea was reported in 24%, 10%, and 4% of patients randomized to Adlyxin, Soliqua and Lantus. Vomiting was reported in 6%, 3% and 2% randomized to Adlyxin, Soliqua and Lantus. Diarrhea was reported in 9%, 9% and 4% for of patients randomized to Adlyxin, Soliqua and Lantus. Adlyxin and Soliqua carry a greater risk of gastrointestinal adverse reactions than Lantus.

**Immunogenicity**
Lixisenatide appears to be highly immunogenic. In the NDA for Adlyxin (NDA208471), approximately 70% of subjects were observed to test positive for lixisenatide anti-drug antibodies (ADA) after treatment with Adlyxin for 24 weeks or more. In this NDA, 43 and 57% had anti-drug antibody to lixisenatide at week 30 in the Soliqua and Adlyxin arm respectively. Subjects with titers above 100 nmol/L were observed to have smaller HbA1c reduction than those with lower titers in non-randomized retrospective analyses (refer to Table 47 in Dr. Balakrishnan’s review).

In trial EFC12404 (insulin naïve population), 21% and 8% tested positive for glargine anti-drug antibodies at week 30. In trial EFC12405 26 and 24% tested positive for glargine anti-drug antibodies at week 30.

_Hypersensitivity/Allergic Reactions/Injection Site Reactions_

In the NDA, 0.6% 0.3% and 0% allergic reaction events were deemed related to the investigational product in the Adlyxin, Soliqua and Lantus arm. The most common adverse allergic reaction terms associated with lixisenatide were urticaria and angioedema (Refer to Table 40 in Dr. Balakrishnan’s review). Injection site reactions were observed in 3%, 3% and 2% of patients randomized to Adlyxin, Soliqua and Lantus in EFC12404 (refer to Table 44 in Dr. Balakrishnan’s review).

**Overall Safety**

Overall the safety analyses revealed that Soliqua carries common risks attributable to both glargine (hypoglycemia) and lixisenatide components (GI-related adverse reaction, allergic adverse reactions, injection site reactions and immunogenicity related risks). Soliqua and Lantus carry a greater risk of hypoglycemia than Adlyxin. Adlyxin and Soliqua carry a greater risk of gastrointestinal adverse reactions than Lantus. Adlyxin and Soliqua carry a greater risk of product related allergic reactions than Lantus. Finally, Soliqua and Lantus carry a greater risk of weight gain than Adlyxin.

**8. Advisory Committee Meeting**

An Advisory Committee meeting was held on May 25, 2016 to discuss the Soliqua application.

The committee members were first asked to discuss whether they would start Soliqua in patients with type 2 diabetes who had not been exposed to either of the two components (lixisenatide and glargine) and to explain why they would or would not use the combination in these patients. Most of the endocrinologists (Burman, Wilson, Seely and Smith) did not see a benefit of the combination in patients naïve to either product and could not identify a patient population of naïve patients for whom this combination would be useful.
Dr. Burman stated: “I think this is really one of the seminal questions and ....I can’t decide in my mind which patients I would start... on this combination.”

Dr. Seely stated; “I’m concerned, in general, about starting two drugs at the same time for several reasons. One is I’m not sure the second one is going to ever be needed or will be needed in the next several years. The second is, there’s usually a substantial increase in cost in a combination drug compared to a single drug.”

Dr. Wilson stated; “I think I’m in the group with one [drug] at a time. Most of us treat metabolic conditions with one [drug] at a time.”

Dr. Smith stated “I share all the concerns and I practice the same way, which is that I have concern about the side effects of one drug when I start that drug. And that is multiplied when one starts two. So I feel a resistance to starting two different agents simultaneously.”

In their rationale the clinical experts stated that most patients naïve to either drug and with HbA1c in the range of ~8-9% could be adequately controlled with addition of a single agent. The choice of agent could be informed by patient preference. If for example fear of weight gain or hypoglycemia was a major concern then use of a single agent with a low likelihood of causing these side effects could be selected (i.e., one of the multiple daily or once weekly GLP-1 agonists). Endocrinologists stated they would not use this drug for patients with really poor HbA1c control (~10%) because insulin dosing needs for patients with severe insulin resistance aren’t likely to be met by Soliqua.

The committee members were asked to discuss the benefits of using the fixed-combination drug product containing lixisenatide and insulin glargine in patients with type 2 diabetes previously treated with either a basal insulin or a GLP-1 agonist i.e. adding a single new drug by using this combination to an existing regimen.

Dr. Burman stated: “I think this is a circumstance where the combination drug would be useful....but I would raise the issue that you’re including in this discussion adding it [to] a GLP-1 agonist where there are no studies on that.”

Dr. Wilson stated: “I think this is probably the [circumstance] where this product would be used. So the type of patient...would be somebody who has been on a metformin, perhaps, most commonly plus a GLP-1 agonist, so now on two drugs. You’ve already got one injection going and the person’s not at goal, probably close to 8 to 9 plus. And this medication is going to bring them down another point, get them close to 7, which is going to be the goal for most patient.”

Dr. Seely stated; “to me [this] is the ideal situation..., that someone’s on a single agent in your combination drug and you want to add the second agent in your combination drug. And you can do it in one delivery. So to me, this would be [the] ideal situation for the combination.”
Drs. Smith and Everett concurred with these opinions.

The committee was then asked to discuss issues related specifically to product presentation and proposed devices, including but not limited to; use errors that may occur in the care setting related to a lack of clarity on the amount of each product delivered with each given dose, insufficient understanding that, unlike insulin products, the maximum dose for the combination is capped, inadequate understanding of the role of the two devices.

The medication error expert, Dr Meisel, voiced the following concerns about the two pen product presentation.

“So I’m very stressed by this issue here with this product in a number of ways and I think I’m also distressed. I understand we need to have educational program [for] 5 million clinicians, but if that’s our safety plan, woe to us because we’re not going to be able to effectively educate 5 million nurses, doctors, pharmacists, pharmacy technicians to know these products while we [...] engineer these errors out of the system. And I haven’t seen anything yet that helps us with that. I think we know, an endocrinologist will know, and [diabetes educators] will know that 30 units of [the] yellow [pen] is not 30 units of [the] green [pen]. But the nurse taking the history at the nursing home, or on the orthopedic floor in the middle of the night, or the medical assistant doing it in the doctor’s office, is going to find out from the patient that she takes 30 units of this drug and the fact that there is [two presentations] and a difference [in dose] between yellow and green, other than color, is going to be lost on them. And so I think that’s hugely concerning to me.”

At the end of the meeting the Advisors were asked if they recommended approval of the fixed combination drug product delivered using the proposed pen devices for the treatment of adult patients with type 2 diabetes. Twelve advisors voted yes and 2 advisors voted no. The two advisors who voted no expressed concerns with the proposed product presentation consisting of two pens. The twelve advisors who voted yes clearly stated in their response that the most appropriate use of this product would be in patients already treated with one component product in the combination. Many of the advisors who voted yes also expressed concerns with the presentation but did not have specific recommendations on how to resolve the issues highlighted in the discussion at the meeting.

9. Pediatrics

Refer to Dr. Chong’s CDTL memorandum for a summary of the pediatric regulatory issues for this application.

10. Other Relevant Regulatory Issues
Regulations at 21 CFR 300.50 describe the Food and Drug Administration’s policy regarding fixed combination drugs as follows:

“Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.”

The approach to the development of fixed combination drug products for the treatment of type 2 diabetes, as laid out in the diabetes guidance document, is consistent with the above regulations and states;

“A fixed-dose combination of a new agent and an established agent should be studied in a manner that demonstrates that each of the individual components makes a contribution to the claimed effects...and that the combination is acceptably safe.”

The claimed effect for a diabetes drug is to improve glycemic control. The additive glucose lowering effect of combining two anti-diabetic agents is usually established either, in a trial enrolling patients who are not at goal on a maximally effective dose of one of the agent in the combination (i.e., sequential “add-on” trials) or in a factorial design study.

The sequential “add-on” trial design more closely mimics the recommended standard of care type 2 diabetes therapeutic algorithm where addition of a second or third glucose lowering agent is recommended if, after some period of time, glucose control remains inadequate for that particular patient. In this paradigm it is assumed that the first agent is still exerting an effect though this is not formally tested (i.e., by withdrawal).

The 2015 American Diabetes Association Standards of Medical Care in Diabetes states that a second agent should be added to a single agent, “if noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months…” This is a sensible approach for two reasons. First, a large proportion of individuals will be adequately treated with addition of a single agent and these patients do not need to be subject to the independent drug-related risks of a second agent. Second, there is no data to suggest patients are placed at increased risk by waiting three months to evaluate whether the single agent gets them to HbA1c goal. In fact, I know of no data that suggest more rapid (measured in months) attainment of ADA glucose goal offers a clinical benefit. In fact, aggressive glucose lowering with polypharmacy with a goal of normalizing glucose levels was associated with increased mortality in the population enrolled in the ACCORD trial. It is important to recall that risks associated with chronic elevation in blood glucose take years to manifest and

---

6 Diabetes Care; Volume 38, Supplement 1, January 2015 and Endocrine Practice. 2015; 21:438-447
are observed in the setting of large differences in glucose control between groups (refer to the landmark trials DCCT and UKPDS).

The factorial trial design compares the glucose lowering effect achieved when two agents are used together to the glucose lowering effect achieved when two agents are used individually. Ideally combinations of all effective doses should be studied. Six\(^7\) possible combinations would have to be studied for a product combining one product with two recommended doses (A) and one with one recommended dose (B). For a product containing a titratable component like insulin designing a study to compare all effective doses is not feasible (i.e., too many possible permutations) and makes no sense from a clinical perspective (i.e., requires patients stay on fixed doses of insulin). The contribution to the claimed effect for Soliqua which contains insulin and is titrated to effect was thus demonstrated on the average dose achieved after titration.

Although the factorial design allows one to establish that initiating any dose of two agents simultaneously will result, on average, in statistically greater glucose lowering than initiating each agent separately over the relatively short term, the factorial trial design does not address more fundamental clinical questions. That is, what clinical benefit is gained from marginally better glucose control over the short term? And is this benefit worth the added risks that come with being exposed to two drugs compared to one? Put in another way, if a subject is able to get to goal with a single agent (an unknown when deciding to initiate dual therapy), why should this patient be subject to the risks of a second agent?

Some in the diabetes community advocate starting two anti-diabetic agents at once in selected patients and the most recent American Diabetes Association therapeutic algorithm recommends “considering” this approach in patients very poorly controlled at baseline [i.e., HbA1c > 9%]. The arguments used to justify a role for initial dual or even triple therapy are based on pathophysiologic theory (i.e., it is better to address multiple metabolic abnormalities at once, two drugs are needed to get to goal when the disease is bad) or logic (i.e., any additional glucose lowering will lead to better outcomes, more rapid glucose lowering is better because it results in increased adherence, fewer office visits, etc.). While some of these arguments may be on their face valid, I know of no empiric data that supports these opinions or recommendations. Combination antidiabetic products are therefore viewed as convenience products whose main role in the therapeutic armamentarium is to reduce daily pill or injection burden in patients requiring two agents.

11. Labeling

I recommend the following indication for Soliqua to ensure safe use of the product.

\(^7\) (i.e., Low dose A + B, High dose A + B, Placebo + B, Low dose A + PBO, High dose A + PBO).
SOLIQUA 100/33 is a combination of insulin glargine and lixisenatide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on a basal insulin (less than 60 units daily) or on lixisenatide.

The tradename, indications and usage section, dosage and administration section of the full prescribing information were edited and optimized to emphasize that Soliqua contains a mixture of two drugs, to ensure prescribers will avoid duplication of therapy with existing GLP-1 receptor agonist products and to provide clear instruction on how to start and dose the product. Patient labeling and carton and container labeling were also optimized to address these issues. See CDTL review for a summary of the labeling changes.

12. Postmarketing

Postmarketing requirement pursuant to the Pediatric Research and Equity Act are discussed in the CDTL memorandum and primary review. No risks identified require risk management beyond labeling to warrant consideration of a Risk Evaluation and Mitigation Strategy (REMS).
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
11/21/2016