Drug Regulatory Affairs

Suliqua®

Summary of the Risk Management Plan (RMP) for Suliqua®
(lixisenatide/insulin glargine)

Document version: 01
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Summary of the risk management plan (RMP) for Suliqua®

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of Suliqua® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Suliqua® in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sanofi-aventis (suisse) is fully responsible for the accuracy and correctness of the content of this published summary RMP of Suliqua®.

1. Overview of disease epidemiology

Diabetes has become a major health concern worldwide. Type 2 diabetes mellitus is the most common type of diabetes and is increasing all over the world. In the European Union, the proportion of the population with type 2 diabetes mellitus ranges from 2% percent up to 24% percent among people over 20 years of age.

Many factors may predispose people to developing type 2 diabetes mellitus. Genetic connections have been identified including family history of diabetes or certain ethnic backgrounds. However, factors related to the lifestyle including excess of calories in the diet, smoking, and alcohol consumption also play an important role in the development of type 2 diabetes mellitus and its complications.

Several complications may occur in patients with type 2 diabetes mellitus including problems in the heart, blood vessels, kidneys, eyes and nervous system which increase a person’s risk of death. Diseases of the heart and blood vessels, also called cardiovascular diseases are the most common cause of death in diabetic patients. This shows importance of following the diet and treatment recommendations from the treating physicians.

2. Summary of treatment benefits

Suliqua® is a combination of insulin glargine, a long acting or basal insulin and lixisenatide, a GLP-1 receptor agonist. It is given by a once daily injection subcutaneously in adult patients with T2DM to improve glycemic control in combination with oral glucose-lowering medicinal products when these alone or combined with basal insulin do not provide adequate glycemic control.

The efficacy and safety of SULIQUA® was demonstrated in two confirmatory studies (active controlled, 30 weeks of treatment) in patients with type 2 diabetes suboptimally controlled on metformin with or without a second oral antidiabetic drug (OAD) (EFC12404), or on established basal insulin with or without 1 to 2 OADs (EFC12405). The efficacy of SULIQUA® was established on the primary efficacy endpoint, change of HbA1c at week 30, and several secondary endpoints.

In both populations studied, treatment with SULIQUA® once daily had a positive benefit-risk balance, better than with each component alone. SULIQUA® significantly decreased HbA1c, thereby allowing more patients to reach HbA1c targets while preventing or minimizing the body weight gain usually observed with initiation or intensification of an insulin-based therapy, and without increasing the hypoglycemia rate compared to insulin glargine alone.
The first study, EFC12404, was performed in \( n = 1170 \) patients insufficiently controlled on metformin alone or with a second OAD. In this population, treatment with SULIQUA® and metformin significantly improved HbA1c from baseline to week 30 in comparison to each component (insulin glargine 100 units/ml or lixisenatide) alone. From similar baseline values of approximately 8.1%, the reductions in HbA1c at week 30 were 1.63% for the SULIQUA® group, 1.34% for the insulin glargine group and 0.85% for the lixisenatide group, reaching mean values of 6.50%, 6.81%, and 7.31%, respectively. The improvement in HbA1c was also reflected in the substantially higher proportion of SULIQUA®-treated patients (73.7%) reaching the prespecified HbA1c target of <7.0% versus patients in the insulin glargine (59.4%) and lixisenatide (33.0%) groups. This occurred without the negative effects on body weight that are typically observed when an insulin-based treatment is initiated. It also allowed more patients treated with SULIQUA® to achieve the composite endpoint of HbA1c responders <7.0% with no weight gain and no hypoglycemia than either component alone.

The second study, EFC12405, \( n = 736 \) patients insufficiently controlled on basal insulin (EFC12405) were randomized after a basal insulin optimization phase. SULIQUA® led to a significant and medically relevant improvement of HbA1c, reaching a value of 6.94% at week 30 compared to 7.48% with insulin glargine (treatment difference -0.52% \( p<0.0001 \)). It allowed more patients to reach HbA1c targets while preventing or minimizing the body weight gain usually observed at intensification of an insulin-based therapy with no additional risk of hypoglycemia as compared to insulin glargine.

3. **Unknowns relating to treatment benefits**

SULIQUA® has been extensively studied in adults with T2DM. However, this medicine has not been studied in children younger than 18 years. Also, there is no experience in patients with severe kidney disease. Therefore the use of this medicine is not recommended in these patients.
4. Summary of safety concerns

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
<th>Preventability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal events ie, nausea and vomiting</td>
<td>The main gastrointestinal side effects with SOLIQUA ie, nausea and vomiting are common. Nausea and vomiting appeared mostly during the first few weeks of the treatment, then decrease with time. They were usually mild to moderate.</td>
<td>As described in the product information, a careful dose titration is required to reduce the risk of gastrointestinal side effects.</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Allergic reactions are uncommon with SOLIQUA. Most of these reported allergic reactions were mild in severity.</td>
<td>Patients with known allergy to SOLIQUA or to any of the components must not take SOLIQUA.</td>
</tr>
<tr>
<td>Hypoglycemia (low blood sugar)</td>
<td>Low blood sugar is a very common adverse effect of SOLIQUA observed in patients.</td>
<td>As described in the product information, patients should be aware of signs and symptoms of low blood sugar (hypoglycemia). A regular monitoring of the blood-sugar level is required while on SOLIQUA. Patients should not skip meals while on this drug. If patients notice signs of low blood sugar, they should take high glucose supplement.</td>
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<tr>
<td>Pancreatitis (inflammation of the pancreas)</td>
<td>Rare cases of pancreatitis have been reported with drugs that work like lixisenatide (a component of SOLIQUA). To date, studies with SOLIQUA have not</td>
<td>Patient should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, SOLIQUA should be discontinued; if acute pancreatitis is</td>
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## Important potential risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known (Including reason why it is considered a potential risk)</th>
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<tbody>
<tr>
<td>Malignant neoplasm</td>
<td>To date, studies with SOLIQUA have not raised concern about an increased risk of cancer. In animal studies with other antidiabetic medications of the same class as lixisenatide (a component of SOLIQUA), development of cancers was observed. It is not known if treatment with lixisenatide could cause cancer in humans.</td>
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<td>Pancreatic cancer</td>
<td>There is currently no evidence from clinical trials that GLP-1 based therapies increase the risk of pancreatic cancer. The numbers of spontaneous reports are limited and in the cases where information is available, confounding factors and/or short-term exposure is common. However, long term consequences of stimulation of beta-cells and suppression of alpha cells as well as possible effects on exocrine pancreas are largely unknown.</td>
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<tr>
<td>Medullary thyroid cancer</td>
<td>To date, studies with SOLIQUA have not raised concern about an increased risk of medullary thyroid cancer. In animal studies with other antidiabetic medications of the same class as lixisenatide, medullary thyroid cancer was seen. No risk of medullary thyroid cancer has been observed in patients treated with lixisenatide.</td>
</tr>
<tr>
<td>Medication errors</td>
<td>Medication errors can occur if SOLIQUA is confused with other injectable insulin products. As instructed in the product information, the label must be checked before each injection to ensure the right medicine is injected. Medication errors can occur if there is confusion between the different ratios of SOLIQUA. As instructed in the product information, the label must be checked before each injection to ensure that the right ratio of SOLIQUA is injected. The adequate pen qualification 10-40 or 30-60 must be checked to ensure the right pen is used. Medication errors can occur if patient takes the wrong dose of SOLIQUA when switched from another injectable diabetes medicine. A similar error in dose could also occur if a patient is switched from SOLIQUA to another injectable diabetes medicine. As instructed in the product information, the label must be checked before each injection to ensure the right ratio of SOLIQUA is injected.</td>
</tr>
<tr>
<td>Immunogenicity/neutralization</td>
<td>Patients may develop antibodies against lixisenatide or insulin following treatment with SOLIQUA. In studies with SOLIQUA, the antibody status was not predictive of safety or efficacy.</td>
</tr>
<tr>
<td>Dehydration/acute renal impairment</td>
<td>If a patient gets dehydrated (risk of loss of body fluids) due to excessive vomiting, it could potentially damage the kidneys (renal impairment). To date, studies with SOLIQUA have not raised concern about an increased risk of dehydration/acute renal failure.</td>
</tr>
<tr>
<td>Risk</td>
<td>What is known (Including reason why it is considered a potential risk)</td>
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<td>Teratogenicity (birth defects)</td>
<td>There is no data on the use of SOLIQUA in pregnant women. SOLIQUA should not be used during pregnancy. Based on animal studies, exposure to lixisenatide during pregnancy may increase the risk of birth defects. The effects of lixisenatide on causing reduced body weight and reduced food consumption can result in fetal defects in animals.</td>
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<tr>
<td>GLP-1: Glucagon-Like-Peptide-1</td>
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**Missing information**

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
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<tr>
<td>Use in pregnancy and lactation</td>
<td>There are no human data from the use of SOLIQUA in pregnant or lactating women. Studies of lixisenatide in animals have shown reproductive toxicity; however, the potential risk for humans is unknown. SOLIQUA should not be used during pregnancy. The use of insulin is recommended instead. If a patient wishes to become pregnant, or pregnancy occurs, treatment with SOLIQUA should be discontinued. It is unknown if SOLIQUA is excreted in human milk. SOLIQUA should not be used during breast-feeding.</td>
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<tr>
<td>Use in children and adolescents &lt;18 years</td>
<td>The safety and efficacy of SOLIQUA in children and adolescents less than 18 years of age has not yet been established.</td>
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<tr>
<td>Use in patients with severe renal impairment (with or without low body weight)</td>
<td>There is no information about use of SOLIQUA with severe kidney disease. SOLIQUA is not recommended in patients with severe renal impairment or end-stage renal disease.</td>
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</table>
5. Summary of additional risk minimization measures by safety concern

The additional risk minimization measures for SULIQUA are discussed in the table below:

**Summary of risk minimization activities by safety concern:**

<table>
<thead>
<tr>
<th>Medication errors including mix-ups between the different strength of the product</th>
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<tbody>
<tr>
<td><strong>Risk minimization measure</strong></td>
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<td>---------------------------------</td>
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</table>
Medication errors including mix-ups between the different strength of the product

- The Pharmacist should clarify with the prescriber any incomplete prescription.
- Explain to your patient that:
  - You are prescribing a number of dose steps which corresponds to a set number of units of insulin plus a fixed amount lixisenatide
  - For Suliqua, one dose step always contains one unit of insulin, regardless of the Suliqua pre-filled pen being used (10-40 pen or 30-60 pen)
  - The dose counter of the pen device shows the number of dose steps to be injected,
- If the patient has been transferred from a different pre-filled pen device, highlight the differences in design between the two devices (focus on colour differentiation, warning statements on carton/label and other safety design features such as tactile elements on the prefilled pen).
- Explain what the patient should anticipate regarding dysglycemia and potential adverse reactions.
- Pharmacists are encouraged to check that patients and caretakers are able to read the strength of Suliqua, the dose range of the pre-filled pen and the dose counter of the pre-filled pen before dispensing insulin glargine/lixisenatide. Pharmacists should also check that patients have been trained on how to use the new pen.
- Patients who are blind or with poor vision must be instructed to always get assistance from another person who has good vision and is trained in using insulin glargine/lixisenatide pen device.
- Tell patients to closely monitor their blood sugar levels when starting insulin glargine/lixisenatide which contains insulin and a non-insulin active substance (lixisenatide).
Risk minimization measure 2

Patient guide

Objective and rationale
To further educate the patients to prevent medication error.

Main additional risk minimization measures (key points)
The Patient guide will contain the following key messages:

- Read the instructions in your package leaflet carefully before using Suliqua.
- Suliqua is supplied in a pre-filled pen and must only be used with this device; patients, carers and healthcare professionals must never use a syringe to withdraw insulin glargine/lixisenatide from a pre-filled pen or dosing errors and serious harm can result.
- Suliqua is available in two pre-filled pens containing two different strengths of lixisenatide, and different dose ranges:
  - Both pre-filled pens contain insulin glargine in a strength of 100 units/mL
  - Suliqua 10-40 pen allows daily doses between 10 and 40 dose steps of Suliqua to be given (strength: insulin glargine 100 units/mL and lixisenatide 50 mcg/mL; dose range: 10 to 40 units of insulin glargine in combination with 5 to 20 mcg lixisenatide)
  - Suliqua 30-80 pen allows daily doses between 30 and 60 dose steps of Suliqua to be given (strength: insulin glargine 100 units/mL and lixisenatide 33 mcg/mL; dose range: 30 to 60 units insulin glargine in combination with 10 to 20 mcg lixisenatide)
- The prescription should mention the pre-filled pen type you need (Suliqua 10-40 pen or 30-80 pen) and the number of dose steps to be injected.
- The Pharmacist should clarify with the prescriber any incomplete prescription.
- One dose step contains one unit of insulin glargine plus a fixed amount of lixisenatide. Before you use insulin glargine/lixisenatide be clear on how many dose steps you require. Your healthcare professional will give you this information.
- For Suliqua, one dose step always contains one unit of insulin, regardless of the

Medication errors including mix-ups between the different strength of the product

- Suliqua pre-filled pen being used (10-40 pen or 30-80 pen).
- Your healthcare professional will explain the design and features of your Suliqua pen, including how the dose counter of the pre-filled pen device shows the number of dose steps to be injected.
- During the switch to this type of combination medicine and in the weeks after the switch you should measure your blood sugar levels more frequently.
- If you have any questions about your treatment speak to your healthcare professional.
6. **Planned post authorization development plan**

**List of studies in post-authorization development plan**

<table>
<thead>
<tr>
<th>Study/activity (including study number)</th>
<th>Objectives</th>
<th>Safety concerns/efficacy issue addressed</th>
<th>Status</th>
<th>Planned date for submission of (interim and) final results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SULIQUA</td>
<td>To demonstrate the superiority of the insulin glargine/lisinatide combination versus GLP-1 receptor agonist and metformin ± pioglitazone in HbA1c change from baseline to week 26.</td>
<td>Additional safety information for all relevant important identified and potential risks</td>
<td>Ongoing</td>
<td>Final study report planned: Q3 2018</td>
</tr>
<tr>
<td>EFC13764 A 28-week open-label study assessing the efficacy and safety of the insulin glargine/lisinatide combination in adults with type 2 diabetes inadequately controlled on GLP-1 receptor agonist and metformin ± pioglitazone</td>
<td>To assess the knowledge and understanding of the key safety messages in the HCP guide and the patient guide for SULIQUA</td>
<td>To assess the trend over a three-year period in knowledge and understanding of the key safety messages in the HCP and patient guides among HCPs and patients, respectively.</td>
<td>Planned</td>
<td>To be determined. Will be provided when the study protocol is finalized and approved.</td>
</tr>
</tbody>
</table>

Survey to evaluate the knowledge and understanding of the key safety messages in the HCP guide and the patient guide for SULIQUA
### 7. Summary of changes to the RMP over time

#### Summary of changes to the RMP over time

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Safety concerns</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>11-Feb-2016</td>
<td>-</td>
<td>Initial RMP</td>
</tr>
<tr>
<td>1.1</td>
<td>08-Aug-2016</td>
<td>Medication errors</td>
<td>Renamed to 'Medication errors including mix-ups between the different strength of the product' based on D120 assessment by CHMP. Additional risk minimization measures to address the risk of medication errors have been included based on D120 assessment report by CHMP. RMP modules have been updated accordingly.</td>
</tr>
<tr>
<td>Version</td>
<td>Date</td>
<td>Safety concerns</td>
<td>Comment</td>
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<td>-------------------------------------------------------------------------</td>
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<tr>
<td>1.2</td>
<td>18-Oct-2016</td>
<td>Medication errors</td>
<td>Additional risk minimization measures to address the risk of medication errors have been updated based on D180 assessment report by CHMP.</td>
</tr>
<tr>
<td>1.3</td>
<td>10-Nov-2018</td>
<td>Medication errors</td>
<td>Key messages of the additional risk minimization measures: “medication”/“medicine” replaced by “insulin glargine/insulin lispro” based on second (D188) joint CHMP and PRAC Response Assessment Report.</td>
</tr>
<tr>
<td>2.0</td>
<td>22-Feb-2017</td>
<td>-</td>
<td>Update for studies reported in Part III, in the context of submission of a variation dossier.</td>
</tr>
</tbody>
</table>

RMP: Risk Management Plan; HA: Health Authority; CHMP: Committee for Medicinal Products for Human Use; PRAC: Pharmacovigilance Risk Assessment Committee.